CT 13/82/01

NCI/ICRDB/CT13 82/01

PB82-938601

ICRDB CANCERGRAM

CLINICAL EVALUATION AND TREATMENT OF MULTIPLE MYELOMA AND OTHER GAMMOPATHIES

SERIES CT13 No. 82/01

JANUARY, 1982

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DIAGNOSIS

1. DETECTION OF J CHAIN IN LYMPHOMAS AND RELATED DISORDERS.

Laurent G, Delsol G, Reyes F, Abbal M, Mihaesco E
(c/o Delsol) Laboratoire d'Anatomie Pathologique, Hopital Purpan, Place du Dr Baylac, 31059 Toulouse Cedex, France
Clin Exp Immunol; 44(3):620-628 1981

Lymph node specimens from 125 patients with malignant lymphomas and related disorders were studied by immunoperoxidase procedure for the presence of intracytoplasmic immunoglobulin (CIg) and J chain. CIg staining was present in 22/24 cases of lymphoplasmacytic-lymphoplasmacytoid lymphomas, and in 10/10 cases of extramedullary plasmacytomas and myelomas. In the majority of these cases J chain could be demonstrated in plasmacytoid or neoplastic plasma cells. In 21/36 cases of immunoblastic lymphomas, intracytoplasmic Ig staining was present. In only two of the 36 cases were the lymphomatous cells stained positively for J chain. J chain was not detected in other lymphomas such as lymphocytic lymphomas, follicular lymphomas, lymphoblastic lymphomas or in Reed-Sternberg cells or hairy cells. J chain was demonstrated in mature plasma cells and immunoblastic cells in hyperplastic lymph nodes, and in angioimmunoblastic lymphadenopathy. These findings show that J chain is not detectable in all B cell lymphomas even in the presence of CIg synthesis, irrespective of class. (Author abstract) (31 Refs)

2. PERIPHERAL NEUROPATHY AND PLASMA CELL NEOPLASIAS: A REPORT OF 10 CASES.

Delauche MC, Clauvel JP, Seligmann M
(c/o Seligmann), Hopital Saint Louis, 75475 Paris Cedex 10, France
Br J Haematol; 48(3):383-392 1981

Ten patients with peripheral polyneuropathy associated with plasma cell neoplasias are reported. Progressive sensorimotor polyneuropathy was the presenting complaint in all patients.

HE 20. 3173/2:

CSF protein concentration was elevated in most patients. The electrophysiological and pathological changes were consistent with a primary segmentary demyelinating disease. All patients were male and younger than the av patient with myeloma. None presented with high tumor mass or overt multiple myeloma. Six were affected with single or multiple plasmacytomas with osteolytic lesions. Unusual hematological features such as polycythemia, thrombocytosis and lymphadenopathy were often combined with the polyneuropathy. Skin hyperpigmentation, gynecomastia and diabetes mellitus were noted in some patients. Complete recovery of the polyneuropathy was observed in some patients after either cyclophosphamide and corticosteroid therapy or radiotherapy of localized plasmacytoma, suggesting a direct relationship between the plasmacytic proliferation and the neuropathy. The nature of the postulated factor produced by the plasma cells and responsible for nerve injury is discussed and the importance of a careful search for plasma cell proliferation in men with obscure polyneuropathies is outlined. (Author abstract) (33 Refs)

3. LIGHT CHAIN NEPHROPATHY.

Tubbs RR, Gephardt GN, McMahon JT, Hall PM, Valenzuela R, Vidt DG

Cleveland Clinic Foundation, 9500 Euclid Ave., Cleveland, OH, 44106
Am J Med; 71(2):263-269 1981

In 13 specimens of renal tissue from 11 patients, deposits of monoclonal immunoglobulin light chains and continuous granular electron-dense material within tubular basement membranes and in association with the glomerular basement membrane were identified. All but one patient were men in the fifth to seventh decades of life, and each presented with azotemia and features of glomerular rather than tubulointerstitital disease. Osteolytic bone lesions occurred in only three patients, and a bone marrow plasmacytosis greater than 30% consistent with plasma cell myeloma was identified in only four patients. Light chain distribution in the nephron was confirmed with immunoelectron microscopy and was not associated with deposition of other serum proteins such as immunoglobulin heavy chains, complement, transferrin, alpha2 macroglobulin and albumin. The electron dense deposits differed in distribution and character from those associated with membranoproliferative glomerulonephritis type II (dense deposit disease), amyloidosis, cryoglobulinemia, macroglobulinemia and benign monoclonal gammopathy. Serum from six of these patients did not bind to normal human or rat renal parenchyma in vitro. Kappa light chain nephropathy was characterized by predominant linear tubular basement membrane kappa deposits, and nodular mesangial and linear glomerular basement membrane kappa immunostaining. Lambda light chain nephropathy was characterized by linear lambda glomerular basement membrane and tubular basement membrane immunostaining. Manifestations of glomerular dysfunction dominated the clinical presentation of light chain nephropathy, and most patients did not have typical features of multiple myeloma. The diagnosis was predicated upon thorough immunohistologic assessment of renal biopsy material. (Author abstract) (25 Refs)

CLINICAL IMMUNOLOGY AND IMMUNOTHERAPY

4. THE SAME TYPE OF CRYSTALLINE INCLUSIONS IN T-LYMPHOCYTES AS IN PLASMA CELLS AND B-LYMPHOCYTES IN MULTIPLE MYELOMA. A PATHOLOGICAL CLONE ORIGINATING FROM A COMMON LYMPHOCYTE STEM CELL?

Stavem P, Forre O

Section Hematology, Medical Dept. A, Rikshospitalet, Oslo, Norway
Scand J Haematol; 26(4):265-271 1981

Two patients with multiple myeloma had the same type of crystals in plasma cells, B-lymphocytes, and T-lymphocytes. It is hypothesized that these crystals are formed in cells belonging to the same clone of pathological cells. The clone would then have to be derived from a common lymphocyte stem cell. (Author abstract) (8 Refs)

5. SUBPOPULATIONS OF T-LYMPHOCYTES IN MULTIPLE MYELOMA.

Pezzutto A, Semenzato G, Agostini C, Raimondi R, Gasparotto G

Policlinico, Via Giustiniani 2, 35100 Padova, Italy
Scand J Haematol; 26(4):333-338 1981

The percentage and absolute numbers of T lymphocytes bearing Fc receptor for IgG and IgM were evaluated in 13 patients with multiple myeloma and in a group of controls of the same age range. An increase in the percentage of TG cells was found, whereas TM cell numbers were not different from those of the controls. In order to better define the properties of the TG lymphocytes, their ability to suppress the PWM-induced B cell differentiation was tested in an in vitro experimental assay. TG cells from multiple myeloma exert a suppressor activity as the TG of the controls in this system. The possible interpretation of suppressor T cell increases in these patients is discussed. (Author abstract) (15 Refs)

6. MULTIPLE MYELOMA ASSOCIATED IDIOTYPE BEARING LYMPHOCYTES: CHARACTERIZATION OF TH E CELL TYPE AND THE ACQUISITION OF AN ENRICHED POPULATION.

Smith LJ

State University of New York, Buffalo, NY
Diss Abstr Int (B); 42(1):148-B 1981

In our studies of eight IgG myeloma patients, we have found that 0-40% of their peripheral blood mononuclear cells exhibited patient specific idiotypic markers. We have extended previous work by subtyping this cell population and by isolating it. Immunofluorescent techniques were used to recognize in various combinations surface idiotypes, Fc(IgG) receptors, IgM-IgD determinants and peroxidase positivity. Rosetting techniques were used with Ficoll Hypaque centrifugation to fractionate cells into resetting and nonrosetting populations. A subpopulation of Fc(IgG) receptor bearing lymphocytes that did not bind sheep RBC was purified by removing the EAET rosetting cells, followed by removal of nylon wool adherent cells. The idiotype bearing cells could be pelleted along with EA but not with EAET or EAC rosetting reagents. After the latter two procedures, cells exhibiting myeloma associated idiotypes were retained at the Ficoll Hypaque interface in enriched numbers. The cell subpopulation obtained by the two step purification method consisted of 90-99% Fc(IgG) receptor bearing lymphocytes of which 17-99% also exhibited the myeloma as-

sociated surface idiotype. Cells with these idiotypic markers thus resembled normal donor peripheral blood lymphocytes that have Fc(IgG) receptors, but lack receptors for sheep RBC. (no Refs)

7. ANTIBODY RESPONSE TO PNEUMOCOCCAL VACCINE IN PATIENTS WITH MULTIPLE MYELOMA.

Schmid CP, Smith RP, Baltch AL, Hall CA, Schiffman G
(c/o Baltch) Infectious Disease Section, Veterans Admin. Medical Center, Albany, NY, 12208
J Infect Dis; 143(4):590-597 1981

Patients with multiple myeloma and Waldenstrom's macroglobulinemia respond poorly to antigenic stimuli and may not be protected by pneumococcal vaccine. Thirty-seven patients and 10 controls received 14-valent pneumococcal capsular polysaccharide vaccine. The patients had lower (p less than 0.01) titers of antibody to 11 of the 12 antigens assayed before vaccination and to 10 of 12 antigens (p less than 0.01) after vaccination than did controls, but the ratios of antibody titers before vaccination to those after vaccination were remarkably similar. A poorer antibody response was observed in patients receiving multiagent chemotherapy than in those receiving chemotherapy with alkylating agents (p less than 0.01 for 6 of the antigens). That these patients did respond to the vaccine (although titers of antibody after vaccination were significantly lower than those in controls) suggests that patients with multiple myeloma or macroglobulinemia may benefit from pneumococcal vaccine. (Author abstract) (28 Refs)

8. DECREASING M SPIKE WITH INCREASING TUMOR BURDEN IN MULTIPLE MYELOMA.

Sahasrabudhe DM, Parker JC
Div. Hematology-Oncology, Univ. North Carolina, Chapel Hill, NC, 27514
Arch Intern Med; 141(9):1152-1153 1981

In a patient with myeloma, the serum concentration of the monoclonal immunoglobulin usually bears a direct relationship with the tumor burden as the disease waxes and wanes. In three cases, the level of the monoclonal protein fell as the plasma cell mass increased. Possible explanations of this observation are discussed. (Author abstract) (5 Refs)

9. T LYMPHOCYTE SUBPOPULATIONS IN THE BONE MARROW AND PERIPHERAL BLOOD OF UNTREATED PATIENTS WITH MYELOMA.

Giustolisi R, Guglielmo P, Rizzo M, Cacciola E
Cattedra di Ematologia, Universita degli Studi di Catania, Via S. Citelli, 95124 Catania, Italy
Ric Clin Lab; 11(2):129-137 1981

T lymphocyte populations were studied in the bone marrow and the peripheral blood of 10 untreated patients (9 men, 1 woman; 50-75 yr old) with multiple myeloma. Total E rosette-forming cell (ERFC) count in the bone marrow was within a normal range in 9/10 patients, while the peripheral blood ERFC was reduced in 9/10. There was a significant decrease of 'high-affinity' (Tha) ERFC in both bone marrow and peripheral blood; 'low-affinity' (Tla) ERFC showed a significant increase in the bone marrow and no changes (compared with control values) in the peripheral blood. These findings indicate that the increase in the Tla (putative suppressor T cells) was absolute in the bone marrow whereas it was relative in the peripheral blood because of a decrease in the Tha level. (36 Refs)

10. IMPAIRED B LYMPHOCYTE FUNCTION IN PATIENTS WITH MALIGNANT LYMPHOMA AND MULTIPLE MYELOMA (MEETING ABSTRACT).

Sieber G, Enders B, Teichmann H, Herrmann F, Ruhl H
No affiliation given
Immunobiol; 159(1/2):28 1981

The generation of immunoglobulin-secreting cells upon stimulation with Pokeweed mitogen (PWM) was studied in patients with malignant lymphoma and multiple myeloma using a reverse hemolytic plaque assay. The experiments revealed that different mechanisms are responsible for the defects of B cell activation and differentiation which are characteristic for these diseases. In Hodgkin's disease the majority of patients with an active stage of the disease exhibited greatly diminished responses of their peripheral B lymphocytes to PWM. In some of these patients suppressor cells were found to cause the unresponsiveness, in others, however, an intrinsic defect of the circulating B cells - sometimes combined with a defective T helper cell capacity - was found. Interestingly, some patients with completely abolished responses of their peripheral B lymphocytes exhibited normal reactivity of their splenic B cells. It could be further shown that the defect of B cell differentiation could be corrected by therapy. In patients with Non-Hodgkin Lymp homa an intrinsic B cell defect was found to be the only cause for the unresponsiveness observed in most of them. In contrast to the patients with Hodgkin's disease the B cell defect could not be corrected by therapy. Isolated T cells of these patients were functionally normal helper cells, and none of the hitherto studied patients had demonstrable suppressor cells in the peripheral blood. We have further studied B cell function in patients with multiple myeloma which have often severe decreased levels of the non-paraproteinemic immunoglobulins in the serum. The experiments revealed that about half of the patients studied had a markedly decreased in vitro B cell reactivity which was due to an intrinsic defect of the cells. Only one patient showed a cell-mediated suppression, whereas humoral suppressive factors in the patients' serum could not be observed. (no Refs)

CHEMOTHERAPY

11. CLASSIFICATION BY STAGE AND RESULTS OF TREATMENT IN MULTIPLE MYELOMA (MEETING ABSTRACT).

Schieppati G, Santoro A, Franchi F
Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Italy
Tumori; 67(2,SupplA):48 1981

In this study we examined 82 consecutive cases of multiple myeloma (multiple myeloma: 62; Bence-Jones myeloma: 13; non-secreting myeloma; 7) treated from January to June, 1979. 11 patients (pat) were stage I (A 11), 14 stage II (A 13, B 1) and 55 stage II (A 48, B 7) (Durie and Salmon). Analysis of the present case series yielded the following survivals after diagnosis (in mo): stage I, 84+; stage II, 42; stage III, 22; A, 36; B, 7. The differences were statistically significant between stages I and II (p less than 0.01) and between pat classified as A and B (p less than 0.01). As for median survival in relation to type of immunoglobulin or light chain produced, a difference was found (p: 0.06) between IgG (39 mo) and IgA (19 mo) forms. 3 schemes of therapy were most used: 1) MP (melphalan 6 mg/square m (sqm)/x days 4 days/po; prednisone 60 mg/sqm/x 4 po, every 4 wk) in 41 pat; 2) MPP (melphalan and

prednisone as in MP; procarbazine 100 mg/sqm/x 10 days/po, every 6 wk) in 14 cases; 3) AP (adriamycin 45 mg/sqm/1 days/iv; prednisone 60 mg/sqm/x 4 days/po, every 4 wk) in 18 cases. In 9 cases other schemes of chemotherapy were used. The percentage of responses obtained was similar in the 3 groups: MP 38 per cent; MPP 54.5 per cent; AP 50 per cent. Prognosis was not influenced by the treatment administered; however, there was a statistically significant difference between responders and non-responders (p less than 0.01). This study confirms: 1) the validity of Durie and Salmon's classification as a prognostic indicator of multiple myeloma; 2) the efficacy of conventional MP therapy compared to other combinations such as MPP and AP; 3) improvement in survival in cases responsive to treatment. (no Refs) (In ITA)

12. MAGNITUDE AND DURATION OF THE RESPONSE TO PROTOCOL M2 IN PREVIOUSLY UNTREATED MYELOMA PATIENTS (MEETING ABSTRACT).

Paccagnella A, Cartei G, Salvagno L, Venturelli E, Chiarion Sileni V, Endrizzi L, Fornasiero A, Fiorentino MV
Ospedale Civile Generale Regionale, Padua, Italy
Tumori; 67(2,SupplA):49 1981

Forty-three patients with multiple myeloma which had not been previously treated received polychemotherapy with M2 (melphalan, carmustine, cyclophosphamide, prednisone, vincristine). 63 per cent were stage III. All of the patients were staged and monitored by calculating the cell mass of the neoplasm by the Durie and Salmon method. An av of 10 cycles of M2 (range 4-13) were administered as induction. Max response was obtained after 3 cycles on the av; in 3 cases only after 10 cycles. 33 patients (77 per cent) achieved a greater than 50 per cent reduction in cell mass and 23 (53 per cent) of them a reduction greater than 75 per cent. Achievement of a stable plateau resulted in suspension of therapy in responders. Diagnosis of recurrence is made when there is a more than 25 per cent increase in tumor mass over the plateau. Total duration of remission (after reaching max response) av 19.5 mo (range 2-70) of which 13.1 mo (range 1-48) were not maintained by therapy. Currently 9/12 patients with recurrence have again responded to M2 for periods of 7 mo (range 3-15); 3/5 patients with recurrences have had a third response to M2. (no Refs) (In ITA)

SELECTED PRE-CLINICAL STUDIES

13. MYELOMA NEUROPATHY: PASSIVE TRANSFER FROM MAN TO MOUSE.

Besinger UA, Toyka KV, Anzil AP, Fateh-Moghadam A, Neumeier D, Rauscher R, Heininger K
Dept. Neurology, Technical Univ. Munich, Munich, W. Germany
Science; 213(4511):1027-1030 1981

Mice were injected daily, for up to 10 wk, with purified monoclonal immunoglobulin G from patients with myelomatous polyneuropathy or benign gammopathy. The animals developed a demyelinating polyneuropathy with slowed nerve conduction velocities. The putative antinerve factor may be an antibody since injection of Fab fragments from the monoclonal immunoglobulin G produced a similar demyelination. This provides evidence of a circulating factor in the serum of myeloma patients with polyneuropathy that reproduces typical features of the human disease on passive transfer. This disorder is thus distinguished from other neuropathies that occur as remote effects of malignant disease but have no identified pathogenic factors associated with them. (Author abstract) (21 Refs)

14. A RAPID PROCEDURE FOR THE ISOLATION OF HUMAN IGM MYELOMA PROTEINS.

Jehanli A, Hough D
Biochemistry Group, Sch. Biological Sciences, Univ. Bath, Bath BA2 7AY, England
J Immunol Methods; 44(2):199-204 1981

A two-step rapid procedure for the isolation of human IgM paraproteins from plas ma samples is described. It involves gel filtration on Ultrogel AcA 34 followed by anion exchange chromatography on DEAE-Sepharose CL6B. The overall yield of IgM is greater than 70% and the final product is pure as judged by immunoelectrophoresis and SDS-polyacrylamide gel electrophoresis. The procedure is applicable to both euglobulin and cryoglobulin IgM proteins of a wide range of electrophoretic mobilities. (Author abstract) (12 Refs)

15. PRESENCE OF STRUCTURALLY ABNORMAL MOLECULES IN MONOCLONAL G IMMUNOGLOBULINS IN HUMAN MYELOMAS.

Malati T, Gupta RM, Chakravorty M
(c/o Gupta) Dept. Pathology, Inst. Medical Sciences, Banaras Hindu Univ., Varanasi 221005, India
Indian J Med Res; 73:930-937 1981

Monoclonal IgGs were isolated from the sera of seven patients with multiple myeloma by ammonium sulfate precipitation and DEAE cellulose column chromatography. Analysis of incidence of class and light chain type showed that three monoclonal proteins were IgG1 type K, three IgG1 type L and one IgG2 type L. Biochemical and biophysical studies revealed the presence of subnormal molecules in three out of seven cases. In one case, a rarely reported aggregated molecule of IgG having 10.32 S value was observed, while in another, a minor peak of a low mol wt IgG of 4.83 S was observed and in the third case, the entire myeloma protein was of low S value 3.94. No antibody activity could be detected against a variety of antigens tested for, including common human commensal and pathogenic flora. Further, there was a preponderance of lambda light chain monoclonal immunoglobulins. These observations lend support to the belief that the plasma cell malignancy in humans may result from genetic predilection rather than from chronic bacterial stimulation. (Author abstract) (23 Refs)

16. BIOLOGICAL ACTIVITY OF THE ANTITUMOR PROTEIN NEOCARZINOSTATIN COUPLED TO A MONOCLONAL ANTIBODY BY N-SUCCINIMIDYL 3-(2-PYRIDYLDITHIO)-PROPIONATE.

Jung G, Kohnlein W, Luders G
Institut fur Strahlenbiologie der Westfalischen Wilhelms Universitat, 4400 Munster, W. Germany
Biochem Biophys Res Commun; 101(2):599-606 1981

The successful crosslinking of neocarzinostatin (NCS) to an IgG1 monoclonal antibody yielding hybrid proteins with biological activity is described. IgG1 is a myeloma protein obtained from the ascites fluid of pristan-treated BALB/c mice. The heterobifunctional reagent N-succinimidyl 3-(2-pyridyldithio)-propionate was used. It was shown that NCS can be linked to monoclonal antibody without loosing its biological activity as measured by the degradation of T2-DNA and bacteriostatic action. Since the hybrid protein still binds to protein A, a drastic change of antibody integrity is unlikely. The antigen binding ability of the hybrid protein, however, remains to be shown. (22 Refs)

17. COMMON NEUROECTODERMAL ANTIGENS ON HUMAN MELANOMA, NEUROBLASTOMA, RETINOBLASTOMA, GLIOBLASTOMA AND FETAL BRAIN REVEALED BY HYBRIDOMA ANTIBODIES RAISED AGAINST MELANOMA CELLS.

Liao SK, Clarke BJ, Kwong PC, Brickenden A, Gallie BL, Dent PB
McMaster Univ., Health Sciences Centre, 1200 Main St., West, Hamilton, Ontario, L8N 3Z5, Canada
Eur J Immunol; 11(6):450-454 1981

The hybridoma system has been utilized to produce antibodies to characterize the cell surface antigens on human melanoma cells. On initial screening, two antibodies derived by the fusion of mouse myeloma cells (SP2/O-Ag14) and splenocytes from a mouse immunized with a melanoma cell line (CaCl 78-1) showed cross-reactivity with 10 melanoma cell lines and did not react with any of 4 epithelial cancer lines, or 4 normal adult fibroblast lines. However, because of reactivity with two neuroblastoma cell lines, additional testing with other neuroectodermal derivatives was carried out and revealed a broad cross-reactivity among melanomas, neuroblastomas, retinoblastomas and glioblastomas and against antigens shared by fetal but not adult brain. Thus, these results indicate the existence of common neuroectodermal antigens on melanoma cells. Before melanoma specificity can be claimed for, an antibody reactivity with nonmelanoma cells bearing these neuroectodermal antigens should be excluded. (Author abstract) (21 Refs)

18. MONOCLONAL ANTIBODIES THAT DEMONSTRATE SPECIFICITY FOR SEVERAL TYPES OF HUMAN LUNG CANCER.

Cuttitta F, Rosen S, Gazdar AF, Minna JD
NCI-VA Medical Oncology Branch, Div. Cancer Treatment, NCI, Washington, DC, 20422
Proc Natl Acad Sci USA; 78(7,part2):4591-4595 1981

Monoclonal antibodies with selectivity for human lung cancer were produced by immunizing BALB/c mice with an established line of human small cell lung cancer (NCI-H69) and fusing the mouse spleen cells to mouse myeloma line X63-Ag8.653. The resulting hybrid cells were initially screened by immunoautoradiography for production of antibodies that would react with NCI-H69 and another small cell lung cancer line (NCI-H128) but not its autologous B-lymphoblastoid line (NCI-H128BL). Stable monoclonal antibody-producing lines were isolated by repeated cloning. Three independently derived monoclonal antibodies, designated 525A5, 534F8, and 538F12, were found to react with three of the major types of human lung cancer (small cell, adenocarcinoma, and squamous carcinoma). They did not react with bronchioloalveolar and large cell lung cancers, myeloma, lymphomas, leukemias, osteogenic sarcoma, mesothelioma, hypernephroma, malignant melanoma, simian virus 40-transformed human fetal lung cells, skin fibroblast lines, human B-lymphoblastoid lines, human RBC, and rodent cells. Interestingly, these antibodies also bound to three out of three human neuroblastomas and two out of three breast cancers but failed to react with mouse neuroblastoma and rat pheochromocytoma. The monoclonal antibodies reacted with human small cell lung cancer tumors obtained at autopsy, but had insignificant reactions with normal human lung, liver, spleen, and skeletal muscle. We conclude that monoclonal antibodies have been generated that react with common antigenic determinants expressed on several human lung cancer types, neuroblastoma, and some breast cancers, but are not detectable by our current assays on a variety of other human tumors or normal adult human tissues. Such antibodies are of potential clinical and biological importance. (Author abstract) (50 Refs)

19. BINDING OF MONOCLONAL ANTIBODIES TO HUMAN BREAST CANCER (MEETING ABSTRACT).

Hendler FJ, Yuan D, Vitetta ES
Departments of Medicine and Microbiology, University of Texas Health Science Center at Dallas, Dallas, TX, 75235
4th Annual San Antonio Breast Cancer Symposium, Nov 6-7, 1981, San Antonio, Texas Cancer Therapy and Research Center of South Texas; 1981

Monoclonal antibodies which react specifically with human breast cancer cells have been generated using hybridoma technology. Two hybridoma cell lines, H59 and H71 were established from the fusion between spleen cells immunized with ZR-75-1 cells, a cloned human breast cell line, and murine myeloma cells. H59 and H71 secrete IgMkappa antibodies which react with glandular estrogen receptor positive breast cancer cell lines, but not with more undifferentiated breast cancer cell lines. Only H71 antibody reacts with a well differentiated breast cancer cell line, T47D, which does not contain estrogen receptors. The H59 and H71 antigens have been isolated by indirect immune precipitation. H59 antigen is a protein complex composed of 2 peptides of approx 30,000 daltons; H71 antigen consists of 2 peptides which are about 28,000 and 2 that are 45,000 daltons. H59 antibody bound to fixed cryosections from 45 of 73 (61.6%) patients with breast cancer; H71 bound to 26 of 53 (49%). Thirty-four percent of specimens reacted with both antibodies while 28.3 percent bound neither antibody. H59 may bind a subset of estrogen receptor positive tumors, whereas H71 bound specimens which do and do not contain estrogen receptors. Both antibodies bound specimens which were progesterone receptor positive and negative. Both antibodies react with most specimens from fibrocystic disease and fibroadenomas. Since both antibodies were identified in differentiated breast cancer cell lines, and benign breast disease, the presence of the antigens in a breast cancer might indicate a more differentiated tumor and be associated with a better prognosis. (no Refs)

20. MONOCLONAL ANTIBODIES REACTIVE WITH HUMAN MAMMARY TUMOR CELLS (MEETING ABSTRACT).

Colcher D, Horan Hand P, Nuti M, Austin F, Schlom J
National Cancer Institute, Bethesda, MD, 20205
4th Annual San Antonio Breast Cancer Symposium, Nov 6-7, 1981, San Antonio, Texas Cancer Therapy and Research Center of South Texas; 1981

Splenic lymphocytes of mice immunized with membrane-enriched fractions of metastatic human mammary carcinoma tissues were fused with the NS-1 non-immunoglobulin (Ig) secreting murine myeloma cell line. This fusion resulted in the generation of hybridoma cultures secreting Igs reactive in solid phase radicimmunoassays with extracts of metastatic mammary carcinoma cells from involved livers, but not to extracts of apparently normal human liver. After further screening of immunoglobulin reactivities and double cloning of cultures, eleven monoclonal antibodies were chosen which demonstrated reactivities with human mammary tumor cells. These monoclonals have been placed into at least five major groups based on their differential binding to the surface of various live human mammary tumor cells in culture, to extracts of mammary tumor tisues, and to tissue sections of mammary tumor cells employing the immunoperoxidase technique. One of the monoclonals was highly reactive in antibody-dependent cell mediated cytotoxicity assays on a variety of human mammary tumor cells in culture. Whereas a spectrum of reactivities to mammary tumors was observed with the eleven monoclonals, no reactivity was observed to apparently normal cells of the following

human tissues: breast, lymph node, lung, skin, testis, kidney, thymus, bone marrow, uterus, thyroid, intestine, liver, bladder, tonsils, stomach, and prostate. None of the monoclonals showed binding to purified ferritin or carcinoembryonic antigen. Monoclonal antibodies of all five major groups, however, demonstrated binding to human metastatic mammary carcinoma cells both in axillary lymph nodes and at distal sites. (no Refs)

21. IMMUNOCHEMICAL STUDIES ON HETEROGENEITY OF IGD MYELOMA PROTEINS.

Ohtani H, Sakaguchi K, Saito M
Dept. Clinical Pathology,, Kitasato Univ., Sch. Medicine, Kitasato 1-15-1, Sagamihara, Kanagawa 228, Japan
Immunology; 43(4):717-722 1981

An antigenic heterogeneity among IgD myeloma proteins was tested by immunoelectrophoresis and double immunodiffusion in agar with four kinds of anti-delta (Fc) antisera produced by immunization with isolated Fc fragments of IgD myeloma proteins. According to antigenicity of the Fc fragment, IgD myeloma proteins were divided into two different groups. Anti-delta(Fc)-Tl(S.T.) antiserum, absorbed with the Y.S. myeloma protein or serum, either gave a faint precipitin line or failed to react against the isolated IgD myeloma proteins or sera. With the papain-digested IgD myeloma proteins and sera, anti-delta(Fc)-Tl antiserum either gave heavy precipitin lines or failed to react. Of twelve papain-digested sera containing I gD myeloma proteins tested, nine (75%) showed positive precipitin lines using anti-delta(Fc)-T1 antiserum. No relationship was found between the two groups of myeloma proteins with respect to IgD levels. SDS polyacrylamide gel electrophoresis of the IgD myeloma proteins (S.T. and Y.S.) showed no difference in the mol wt of the whole myeloma proteins, and their light and heavy chains. Polyacrylamide gel electrophoresis of the IgD myeloma proteins (S.T. and Y.S.), after treatment with papain, revealed almost the same patterns. (Author abstract) (5 Refs)

22. DESCRIPTION OF THE NATURAL ANTITUMOR RESPONSE IN BALB/C MICE BY MEANS OF MONOCLONAL ANTIBODIES (MEETING ABSTRACT).

Miotti s
No affiliation given
Tumori; 67(2,SupplA):168 1981

In the sera of various mouse strains natural cytotoxic antilymphoma antibodies have been found whose biological and biochemical characterization have been made difficult by their low affinity and by the low antibody titer. It has been possible to overcome this obstacle by creating cell hybrids between murine myeloma P3 and normal non-immune BALB/c lymphocytes from animals selected for their high natural antitumor response. The supernatants of the hybridomas produced in different fusions were tested with the complement-mediated cytotoxicity tests on tumor cells (EL-4) and normal cells (thymus). At the end of screening 4 hybridomas turned out to produce cytotoxic antibodies only for the tumor cells and these were later characterized. Hybridoma A6 produces IgG 2, cytotoxic for cells infected with murine ecotropic virus and which recognize an 80K mol wt protein on the membrane of tumor EL-4 on immunoprecipitation. The other 3 monoclonal antibodies, C2, B3, and D1, belong to the IgM class. Monoclonal C2 recognizes an antigen present on fetal liver cells in addition to certain lymphomas, but not in bone marrow or adult thymus. From a biochemical standpoint we are dealing with a 26K mol wt identified by affinity chromatography. Monoclonal antibody B3 recognizes a structure probably related to the presence of endogenous virus; however, it is negative in virus-induced tumors while being positive in a whole series of tumors induced by carcinogenic chemicals. In affinity chromatography more than one protein is bound by the antibody and various hypotheses have been formulated to explain this phenomenon. The fourth monoclonal antibody D1, is directed against a molecule present in lymphomas of various origin besides those on the membrane and in the cytoplasm of normal fibroblasts. However, it is not detectable on normal lymphoid tissue and barely represented on transformed fibroblasts. (no Refs) (In ITA)

23. CONDITIONS REQUIRED FOR THE INHIBITION OF IN VITRO GROWTH OF A MOUSE MYELOMA CELL LINE BY ADHERENT BONE-MARROW CELLS.

Ziporl D
Dept. Cell Biology, Weizmann Inst. Science, P.O. Box 26, 76100 Rehovot, Israel
Cell Tissue Kinet; 14(5):479-488 1981

The in vitro growth of the MPC-11 myeloma cell line was inhibited when these cells were co-cultured with adherent cells from mouse bone marrow. This growth inhibition involved prolongation of the specific population doubling time of the MPC-11 cell line. Control cultures of MPC-11 cells exhibited an av doubling time of 14-15 hr, whereas in the presence of adherent layers the length of the doubling time was up to 28 hr. This prolongation in the doubling time did not depend on the duration of incubation, but on the relative proportions of tumor cells and adherent cells employed. MPC-11 cells seeded in relatively high starting cell concentrations partially overcame the growth inhibition. The inhibitory activity of adherent cells from the bone marrow did not appear to be due to production of soluble factor(s), since media conditioned by adherent cells did not affect cell growth. Moreover, in modified cocultures in which MPC-11 cells grew physically separated from the adherent layers, only marginal growth inhibition activity was observed. The possibility that cell-to-cell interactions lead to the inhibition of growth of MPC-11 cells by adherent cells from the bone marrow, and the implications of these findings to the control of cell growth by the hemopoietic microenvironment, are discussed. (Author abstract) (13 Refs)

REVIEWS

24. MULTIPLE MYELOMA.

Early AP, Ozer H, Henderson ES
Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
NY State J Med; 81(6):883-893 1981

Multiple myeloma is a neoplastic proliferation of plasma cells producing in most instances a specific, monotypic immunoglobulin. Osteoclast-activating factor(s) secreted by the neoplastic plasma cells mediates focal and generalized osteolysis. Synthesis of normal, polyclonal immunoglobulins is decreased, and there is frequently suppression of erythropoiesis, granulopoiesis, and megakaryocytopoiesis. Recent investigations have implicated involvement of several cell populations and immunoregulatory mechanisms in the pathogenesis of the disease. Clinical features include bone pain, anemia, increased susceptibility to infection, renal insufficiency, and hypercalcemia. Less frequent but significant complications include spinal cord and

nerve root compression, neuropathy, hyperviscosity syndrome, amyloidosis, and extraosseous plasma cell tumors. The diagnosis is established by demonstration of a monoclonal serum and/or urine paraprotein in association with decreased levels of normal polyclonal immunoglobulins, marrow plasmacytosis, and osteolytic bone lesions. Chemotherapy has ameliorated symptoms and prolonged survival. Melphalan, given continuously or in intermittent high dose, in combination with prednisone remains the treatment of choice. Clear benefit from multiagent chemotherapy remains to be established. Prognosis is poor for those patients who fail to respond or relapse but several therapies now under investigation may be of benefit. The underlying principle for management of disease complications is control of the myelomatous process, although supportive measures such as plasmapheresis or local radiotherapy may be essential. Future advances depend on unravelling the extent of the myelomatous process and defining the disease's immunoregulatory mechanisms. (Author abstract) (176 Refs)

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CLINICAL EVALUATION AND TREATMENT OF MULTIPLE MYELOMA AND OTHER GAMMOPATHIES

SERIES CT13 No. 82/02

FEBRUARY, 1982

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DIAGNOSIS

1. EYE INVOLVEMENT IN MULTIPLE MYELOMA.

Giarelli L, Melato M, Campos E, Falconieri G
(c/o Melato) Istituto di Anatomia e Istologia Patologica, Universita di Modena, Ospedale Maggiore, via Pieta 2/2, 34125 Trieste, Italy
Haematologica (Pavia); 66(1):57-67 1981

Frequency and type of involvement of eye structures were investigated in 18 cases (6 male, 12 female; 39-87 yr old) in which histopathological diagnosis at autopsy confirmed the presence of multiple myeloma (MM). Complete results were obtained in 13/18 patients. In 9 cases clinical follow-up was possible, so that mean survival of 19 mo was found from the time of diagnosis, with a range of 1 mo-5 yr. Varying patterns of amyloid deposition in the heart, kidney, liver, and eye were observed. Seven pairs of eyeballs showed the presence of neoplastic plasma cells; infiltration particularly involved the chor oid in five cases. Other findings included: plasma cells invading the ciliary body and associated with severe reactive processes such as ossification (1 case), inflammation mainly localized to the choroid (3), panophthalmitis (1), isolated plasma cells present in the preretinal portion of the vitreous (2), cysts of the pars plana retinae (3), eye involvement by amyloidosis, of the

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vascular type (5), and cavernous degeneration of the optic nerve (1). (23 Refs)

CLINICAL IMMUNOLOGY AND IMMUNOTHERAPY

2. POLYVALENT PNEUMOCOCCAL IMMUNIZATION OF PATIENTS WITH PLASMA CELL DYSCRASIAS.

Shildt RA, Rubin RR, Schiffman G, Giolma P
Oncology Service, Brooke Army Medical Center, Box 517, Beach Pavilion, Fort Sam Houston, TX, 78234
Cancer; 48(6):1377-1380 1981

Thirteen patients with plasma cell dyscrasias and 27 healthy adults were immunized with polyvalent pneumococcal vaccine. Antibody responses were determined by radioimmunoassay. Patients with plasma cell disorders had significantly lower preimmunization and postimmunization antibody titers compared with those of the controls (p-0.01 and 0.008, respectively). Even though the overall response in myeloma patients was poor, occasional rises in antibody titers occurred. Immunizing myeloma patients with the pneumococcal vaccine is recommended. (Author abstract) (16 Refs)

3. THE STUDY OF THE BONE MARROW T-LYMPHOCYTES SUBSETS IN THE MULTIPLE MYELOMA PATIENTS.

Rizzo M, Meli C, Bonnano M, Maccarrone S, Guglielmo P
Cattedra di Ematologia, Universita di Catania, Catania, Italy
Boll Soc Ital Biol Sper; 57(6):678-684 1981

The purpose of this study was to find out, if the presence of the myelomatous B-monoclonal component could be associated to the changes in the T-dependent lymphocyte compartment. The 10 multiple myeloma (MM) patients (50-75 yr old) were compared with 12 normal controls. The total E-rosette forming T-cells (ERFC) were in the normal range (9.2 av MM, 10.3 av controls), except for one case with reduced value. Using West method quantitative distribution of the two main T-lymphocyte subsets was accomplished. High-affinity ERFC were reduced (2.13 av MM, 9.00 av controls) and low-affinity ERFC were increased (7.10 av MM, 3.00 av controls). Surface and intracytoplasmic immunoglobulins determination showed an inverse relationship between the B-monoclonal malignant component and low-affinity ERFC in all the patients. The predominance of the low-affinity T-subsets could play a role in the regulation of the myelomatous B-monoclonal component growth rate. (22 Refs) (In ITA)

CHEMOTHERAPY

4. PEPTICHEMIO IN MULTIPLE MYELOMA (PRELIMINARY RESULTS).

Cavo M, Gobbi M, Tura S
(c/o Gobbi) Istituto de Ematologia, Policlinico S. Orsola, via Massarenti, 9, 40138 Bologna, Italy
Haematologica (Pavia); 66(2):208-215 1981

Twenty-three multiple myeloma cases were treated with peptichemio plus prednisone (PcP) in order to assay oncostatic activity. Clinical, hematological, and preliminary tumor mass effects are described. Of 19 evaluable patients, 11 showed tumor mass reduction, 7 remained stable, and in 1 the disease advanced. Thirteen patients showed improved performance status. Of 8/11 evaluable, previously untreated patients, 5 responded to PcP but only 1 exhibited greater than 50% tumor mass reduction. Six of the eight patients showed significant improvement in performance status. Of 3/4 evaluable patients treated unsuccessfully with MP (melphalan plus prednisone), two remained stable following PcP treatment and one showed disease progression; performance status improved in only 1/3 patients. Of eight patients who relapsed after long (10-22 cycle) MP treatment, six responded to PcP treatment (three with greater than 50% tumor mass reduction) and two remained stable. Performance status improved in 6/8 patients. Phlebitis occurred in three patients following PcP treatment; severity caused cessation of therapy in only one patient. Hematologic side effects of PcP were observed in eight patients, five previously untreated and three who had relapsed after MP treatment; anemia developed more frequently than neutropenia or thrombocytopenia. Treatment was discontinued due to severe myelosuppression in only one patient. Results indicated that PcP can be an effective drug in the treatment of multiple myeloma; lack of cross resistance between peptichemio and melphalan was evident. (16 Refs)

5. AGGRESSIVE PLASMA CELL MYELOMA. A TERMINAL PHASE.

Suchman AL, Coleman M, Mouradian JA, Wolf DJ
(c/o Coleman) Div. Hematology-Oncology, Dept. Medicine, New York Hosp.-Cornell Medical Center, 525 E 68th St., New York, NY, 10021
Arch Intern Med; 141(10):1315-1320 1981

Seven patients with plasma cell myeloma experienced an aggressive, terminal phase. This phase is characterized by rapidly enlarging soft-tissue masses with tumor morphologic characteristics similar to a poorly differentiated or large-cell (histiocytic) lymphoma, with rapid death, and often with fever, pancytopenia, decreasing levels of myeloma protein, and younger age. Median survival from the onset of the phase was 4 mo. There was no response to single-agent or combination chemotherapy. In view of the extremely poor prognosis and lack of response to conventional treatment, patients experiencing this characteristic terminal phase should be considered candidates for innovative therapy. (Author abstract) (22 Refs)

6. DRUG RESISTANCE IN MULTIPLE MYELOMA ASSOCIATED WITH HIGH IN VITRO INCORPORATION OF 3H-THYMIDINE.

Hofmann V, Salmon SE, Durie BG
(c/o Durie) Section Hematology and Oncology, Dept. Internal Medicine, Coll. Medicine, Univ. Arizona Health Sciences Center, Tuscon, AZ, 85724
Blood; 58(3):471-476 1981

In multiple myeloma, tumor cell mass and labeling index correlate with subsequent survival duration, but do not predict for response to treatment. In the present study we have autoradiographically measured the incorporation of 3H-thymidine as determined by the number of grains over the myeloma nuclei in bone marrow aspiration samples. In 33/37 patients with less than 50% tumor regression or progressive disease, the pretreatment grain count was greater than or equal to 20/myeloma nucleus. Conversely, values of less than 20 were found in 27/29 patients who had greater than or equal to 50% cell mass reduction. Survival duration was significantly better (p less than 0.001) in patients with grain counts less than 20. Sixty per-

cent of the patients with both a low labeling index (less than or equal to 3%) and grain count (less than 20) were alive at 48 mo, whereas 15/17 patients with a high labeling index and grain count had a median survival of less than 6 mo. In a subset of 22 patients, there was a significant correlation between in vitro resistance to melphalan, adriamycin, and vincristine as tested in the myeloma stem cell colony assay system and a grain count of greater than 20. We can only speculate as to the reasons for the increased 3H-thymidine uptake by myeloma cells resistant to treatment, however, it could be associated with accumulation of excess DNA and/or increased unscheduled DNA synthesis following injury from alkylating agents. (Author abstract) (26 Refs)

RADIOTHERAPY

7. EXTRAMEDULLARY PLASMACYTOMA OF THE HEAD AND NECK.

Bush SE, Goffinet DR, Bagshaw MA
Cancer Res. and Treatment Center, Univ. New Mexico Sch. Medicine, 900 Camino de Salud, Albuquerque, NM, 87131
Radiology; 140(3):801-805 1981

Extramedullary plasmacytoma of the head and neck is an uncommon plasma-cell neoplasm that arises most frequently from the soft tissues of the upper airways. Ten patients with extramedullary plasmacytoma of the head and neck received primary external beam megavoltage radiotherapy with doses between 4,000 rad (40 Gy)/29 days and 6,075 rad (60.75 Gy)/42 days. In eight patients the disease was locally controlled, although distant spread of the disease subsequently developed in four of them. Observations of the patients' medical histories, their response to treatment, and patterns of relapse suggest that extramedullary plasmacytoma is a separate clinicopathologic entity from other plasma-cell tumors and is appropriately managed by local irradiation (Author abstract) (16 Refs)

CASE REPORTS

8. MULTIPLE MYELOMA ASSOCIATED WITH MYELOFIBROSIS. REPORT OF A CASE AND LITERATURE REVIEW.

Kasimis BS, Lin RY, Neiman RS
Section Hematology-Oncology, Veterans Admin. Hosp., 5901 East Seventh St., Long Beach, CA, 90822
Oncology; 38(6):369-372 1981

A case of multiple myeloma associated with myelofibrosis and myeloid metaplasia is reported. The presentation of our patient and a detailed review of the current literature suggest that more than a chance relationship exists between the two disorders. The role of chemotherapy in the induction of bone marrow fibrosis appears to be unlikely. (Author abstract) (16 Refs)

9. MYELOMA PROTEIN SYNTHESIS WITHIN THE CNS BY PLASMA CELL TUMORS.

Siegal T, Shorr J, Lubetzki-Korn I, Soffer D, Naparstek E, Tur-Kaspa R, Abramsky O
Dept. Neurology, Hadassah-Hebrew Univ. Hosp., P. O. Box 12000, Jerusalem 91220, Israel
Ann Neurol; 10(3):271-273 1981

The cases of two patients with CNS involvement from plasma cell tumors are reviewed. One (a 72-yr-old woman) had leptomeningeal infiltration and the other (a 67-yr-old woman) had solitary intracranial plasmacytoma. Both had been previously diagnosed as having multiple myeloma, for which myeloma monoclonal protein is a tumor marker. The presence of monoclonal bands in the cerebrospinal fluid (CSF) and an elevated IgG index (CSF/serum IgG and CSF/serum albumin ratio) indicated the presence of secreting myeloma cells in the CNS. Other reports exist in the literature that also indicate the value of electrophoretic CSF studies in both diagnosis and follow up of patients with multiple myeloma in whom subsequent CNS tumors are suspected from clinical presentation. (15 Refs)

SELECTED PRE-CLINICAL STUDIES

10. A VARIANT OF THE DEXTRAN-BINDING MOUSE PLASMACYTOMA J558 WITH ALTERED GLYCOSYLATION OF ITS HEAVY CHAIN AND DECREASED REACTIVITY WITH POLYMERIC DEXTRAN.

Matsuuchi L, Wims LA, Morrison SL
Dept. Microbiology, Columbia Univ., Coll. Physicians and Surgeons, New York, NY, 10032
Biochemistry; 20(17):4827-4835 1981

Variants have been isolated from the J558 BALB/c mouse myeloma (IgA, lambda; anti-alpha1 3dextran) that are producing immunoglobulin Ig altered in reactivity with polymeric dextran. In this report, one spontaneously raising mutant, L187, is characterized in detail. The Ig produced by L187 was indistinguishable in mol wt from that of J558; however, a difference in charge between the two proteins was observed and could be localized to the Fab portion of the molecule. Peptide map analysis failed to shown any differences between the amino acid content of the proteins; instead, the carbohydrate content of the chains differs. Examination of the glycopeptides derived from J558 and L187 Igs showed that L187 glycopeptides contain more sialic acid. Altered glycosylation apparently was the consequence of altered glycosyl-transferases within the two cell lines. Comparison of the glycopeptides from the glycoprotein G of vesicular stomatitis virus (VSV) grown in mutant and wild-type cells shows that the mutant and wild-type cells differ in t heir cellular glycosyltransferases. Somatic cell hybrids between either L187 or J558 and MPC-11 (4T001) also demonstrate that in the proper cellular environment the J558 protein could contain large amounts of sialic acid. J558 protein, synthesized in the hybrids and containing sialic acid, bound antigen less well than did wild-type J558 protein and identically with L87 protein synthesized in the somatic hybrids. L187 Ig does not react with polymeric dextran as well as does J558 Ig. However, the mutant Ig appears to have the same reactivity pattern with oligosaccharides as does J558, and thus the size of its antibody combining site does not appear to differ from that of J558. L187 shows that different myeloma cell lines and mu-

tants may have different glycosyltransferases available and provides the first demonstration that the carbohydrate content of an Ig molecule can influence its reactivity with antigen. (Author abstract) (52 Refs)

11. RAT IGD MYELOMA PROTEIN: CELL-FREE TRANSLATION OF THE DELTA MRNA AND BIOCHEMICAL ANALYSIS OF INTRACELLULAR AND MEMBRANE DELTA CHAIN.

Sire J, Alcaraz G, Bourgois A, Jordan B
Centre d'Immunologie INSERM-CNRS de Marseille-Luminy, Case 906, F-13288 Marseille Cedex 9, France
Eur J Immunol; 11(8):632-636 1981

The analysis of IgD molecules produced by the tumor-derived IR 731 cell line showed that these molecules are not secreted and are only present at the cell surface as covalent dimers of 48,000 dalton delta chains. The original IR 731 tumor secreted complete IgD; thus, the disappearance of secretion in the cell line was correlated with the absence of light chain synthesis. The mRNA coding for the cell line delta chain was isolated and translated. The analysis of the translated delta chain (mol wt: 40,000) confirmed the absence of a region having the size of a domain as previously shown by partial amino acid sequence. The observation that the absence in delta chain of this region, which comprises most of the CH2 domain, could be a general feature of murine species is discussed. (Author abstract) (48 Refs)

12. QUANTITATIVE IMMUNOFLUORESCENT ANALYSIS OF SURFACE PHENOTYPES OF MURINE B CELL LYMPHOMAS AND PLASMACYTOMAS WITH MONOCLONAL ANTIBODIES.

Lanier LL, Warner NL, Ledbetter JA, Herzenberg LA
Immunology Lab., Dept. Pathology and Medicine, Univ. New Mexico Sch. Medicine, Albuquerque, NM, 87131
J Immunol; 127(4):1691-1697 1981

In this study, a large series of murine B lymphomas and plasmacytomas were examined by quantitative flow cytometry analysis using a panel of monoclonal antibodies against murine differentiation antigens. These cell lines appear to represent subpopulations of lymphoid cells arrested at distinct stages of differentiation. In general, the pattern of reactions of these monoclonal antibodies with the B cell neoplasms was comparable to the reactions seen with normal cells in the same lineage. The Thy-1.2, Lyt-2, and T-30 differentiation antigens were not detected on any B lymphoma or plasmacytoma. However, certain surface Ig-positive B lymphomas do express the Lyt-1 antigen. With respect to other differentiation markers examined, including E2, F1, ThB, Lgp-100 (Ly 9.1), G2, and T-200 (Ly 5), the reaction of the B cell tumors reflected the expression of these markers on comparable normal cells. This investigation also emphasized the marked intratumor and intertumor heterogeneity that is observed when cloned cell lines are analyzed quantitatively for a large number of surface markers. Thus, this approach may be particularly useful in defining heterogeneity in maturation states within cloned tumor cell lines. (Author abstract) (33 Refs)

13. RECOGNITION OF MOPC-460 VARIABLE REGION DETERMINANTS BY POLYCLONALLY DISTRIBUTED TRIGGERING RECEPTORS ON B LYMPHOCYTES.

Primi D, Juy D, Le Guern C, Sanchez P, Cazenave PA
Unite d'Immunochimie Analytique, Institut Pasteur, 28 rue du Dr. Roux, 75724 Paris Cedex 15, France
J Immunol; 127(4):1714-1718 1981

Purified M460 protein-induced untreated and anti-Thy 1.2 and complement-treated murine spleen cells to proliferate and differentiate in vitro. Fc receptor complexing was not responsible for the phenomenon, since M460 Fab fragments retained the B cell triggering activity. Activation was inhibitable by the addition of DNP-glycine to cultures and could also be detected by using spleen cells from various strains of mice, including the C3H/HeJ, which is genetically nonresponding to LPS. Hybrid molecules were constructed between the M460 proteins and the products of two myelomas that do not activate B cells, namely, X25 and X24. The only hybrid molecules that retained triggering activity were (L460-HX25)2. Interestingly, the same molecule was also the only one recognized by an anti-M460 monoclonal antibody (F6(5:)) that has been previously shown to induce B cells to proliferate and differentiate. The data suggest the existence on B lymphocytes of a network of polyclonally distributed mitogen receptors that share determinants cross-reacting with Ig idiotypes. (Author abstract) (21 Refs)

14. GENETICS OF SUSCEPTIBILITY TO PRISTANE-INDUCED PLASMACYTOMAS IN BALB/CAN: REDUCED SUSCEPTIBILITY IN BALB/CJ WITH A BRIEF DESCRIPTION OF PRISTANE-INDUCED ARTHRITIS.

Potter M, Wax JS
Lab. Cell Biology, NCI, Bethesda, MD, 20205
J Immunol; 127(4):1591-1595 1981

BALB/cAn and BALB/cJ inbred strains of mice were separated 43 yr ago, but are still very closely related because they carry the same allelomorphs at many loci. When injected 3x ip with 0.5 ml of pristane (2, 6, 10, 14 tetramethylpentadecane) 11% of strain BALB/cJ develop plasmacytomas in contrast to 61% in BALB/cAn sublines. BALB/cJ first injected with pristane as neonates also developed a redu ced number of plasmacytomas as compared with BALB/cAn. About 20% of pristane-treated BALB/cAn and 70% of pristane-treated BALB/cJ develop arthritis, which first appeared in the ankle joints after a latent period of 4 mo or more. (Author abstract) (32 Refs)

15. T CELLS WITH FC RECEPTORS FOR IGA: INDUCTION OF TALPHA CELLS IN VIVO AND IN VITRO BY PURIFIED IGA.

Hoover RG, Dieckgraefe BK, Lynch RG
(c/o Lynch) Dept. Pathology (ML-144), Univ. Iowa Hosp., Iowa City, IA, 52242
J Immunol; 127(4):1560-1563 1981

Previous studies demonstrated that BALB/c mice with the IgA-secreting plasmacytomas MOPC-315 (alphalambda2), MOPC-167 (alphakappa), McPC-603 (alphakappa) and TEPC-15 (alphakappa) developed large numbers of T cells with surface membrane receptors for IgA (Talpha cells). The lack of Talpha cell expansion in mice with variant plasmacytomas that were nonsecretors or low secretors of IgA implied that elevated serum IgA contributed to the increase in Talpha cells. The present studies showed that normal BALB/c mice that were given daily injections of 30 mg of IgA (M315 protein) develop

a marked increase in the number of Talpha cells. These studies also show that the Talpha cells induced by injection of IgA are Lyt1-2+ T cells. In addition, the data presented demonstrate that nylon wool nonadherent T cells, treated with purified polymeric IgA (M315 protein) in vitro, develop a marked increase in the number of Talpha cells. The in vitro induction of Talpha cells by IgA requires DNA and protein synthesis. These findings indicate that Talpha cell expansion observed in mice with IgA myeloma is related to the high serum level of IgA and not to the myeloma tumor per se. In addition, these observations have a more general relevance to the issue of B cell regulation because they demonstrate that secreted Ig can directly induce expansion of immunoregulatory T cells. (Author abstract) (17 Refs)

16. INDUCTION OF TUMOR RESISTANCE IN MICE BY HYBRID CELL LINES BETWEEN HUMAN ACUTE LEUKEMIA AND MOUSE MYELOMA CELLS.

Kawashima K, Watanabe E, Isobe K, Suzuki H, Kato Y, Minami S, Nagura E, Ogura M, Yokomaku S, Yamada K, Nagai Y, Takahashi T

First Dept. Internal Medicine, Nagoya Univ., Sch. Medicine, Showa-ku, Nagoya 466, Japan

Igaku No Ayumi; 117(9):770-772 1981

Three hybrid cell lines were obtained from human acute lymphatic leukemia (ALL) and BALB/c mouse myeloma cells (NS-1). They were morphologically all lymphocytic. Absorption tests revealed that they lacked human leukocyte antigen (HLA)-A9 which was expressed in the human ALL cells. Chromosomal analysis showed clone 5 to be diploid, and clones 6 and 12 to be tetraploid, with 1-9 of the D, E, F, and G group human chromosomes. When 5 x 10(6) clone-5,-6, and-12 cells were injected into BALB/c nu/nu mice sc, all the mice developed tumors (at least 0.5 x 0.5 cm) within 2 wk just as did those injected with the NS-1 tumor, and they later died. However, when 1 x 10(7) cells of clones 5, 6, and 12 were injected into BALB/c mice sc, tumors developed in 5/10, 8/10 and 9/10 mice, respectively and, although the tumors were as large as 1.5 cm in some of the mice, the tumors regressed naturally within 1 mo in all of the mice. All of the control mice that were injected with NS-1 tumors developed tumors and 9/10 died within 2 mo. When the BALB/c mice that had been injected sc with 5-10 x 10(6) hybrid cells and had rejected them were challenged by 5 x 10(6) NS-1 tumor cells sc, although tumors were produced in some of the mice in each group almost all the tumors regressed naturally, and tumor deaths occurred in only 2/10, 0/5 and 0/10 of the mice immunized with clones 6, 5 and 12, respectively. When 5 x 10(6) BALB/c-derived Meth-A tumor cells were injected into the mice that were resistant to NS-1 tumors, all of the mice died as did the control mice, the resistance being immunospecific. (10 Refs) (In JPN)

17. THE USE OF LYMPHOCYTES FROM AXILLARY LYMPH NODES OF MASTECTOMY PATIENTS TO GENERATE HUMAN MONOCLONAL ANTIBODIES.

Wunderlich D, Teramoto YA, Alford C, Schlom J (c/o Schlom) Lab. Cellular and Molecular Biology, NCI, NIH, Bethesda, MD, 20205

Eur J Cancer Clin Oncol; 17(7):719-730 1981

Lymphocytes from axillary lymph nodes of breast cancer mastectomy patients were fused with murine non-Ig-secreting myeloma cells to generate hybridoma cell lines that synthesize human Ig. Lymph node lymphocytes from 21 patients were used to obtain 505 human-mouse hybrid cultures. From these, 62 cultures were established which synthesized Ig reactive in radioimmunoassays specific for either IgG or human IgM. Some of these double-cloned hybrid cell lines produced human monoclonal antibodies for at least 6 mo. Sodium dodecylsulfate polyacrylamide gel electrophoresis and immunodiffusion analysis demonstrated that the monoclonal antibodies possessed human heavy and light Ig chains. Levels of synthesis ranged from 0.1 to 20 ug of human Ig per ml of culture fluid. The immunoreactivity of some of these human monoclonal antibodies with mammary carcinoma cells is summarized and has been documented elsewhere; the reactivity of the majority of the Ig, however, is still unknown at this time. The studies reported here detail the procedures in which axillary lymph nodes from mastectomy patients are used in the generation of human-mouse hybridomas that synthesize human monoclonal antibodies. (Author abstract) (14 Refs)

18. SPECIFICITY OF A MONOCLONAL ANTI-K 562 ANTIBODY.

Schienle HW, Muller-Ruchholtz W

Dept. Immunology, Univ. Kiel, Brunswiker Strasse 2-6, D-2300 Kiel, W. Germany

J Cancer Res Clin Oncol; 101(1):109-110 1981

Clone cells secreting an IgG antibody were obtained by immunizing female BALB/c mice with normal bone marrow cells and then hybridizing the mouse spleen cells with myeloma cells. The monoclonal antibody reacted preferentially with the K 562 cell line established from the pleural exudate of a patient in chronic myelocytic leukemia blast crisis. Weekly positive reactions were seen with a B-cell line (Daudi) and a monocyte cell line (U 937). The antibody, therefore, appears to define an antigen present on pluripotent stem cells in a high concentration and on slightly more differentiated precursor cells in a low concentration. (7 Refs)

19. CELL HYBRIDIZATION: A MONOCLONAL MARKER AS A DIAGNOSTIC AID IN HEMATOLOGY AND ONCOLOGY.

Tilz GP, Beverley P, Becker H, Lanzer G, Sedlmayr P

Medizinische Universitatsklinik, Auenbruggerplatz 15, A-8036 Gratz, Austria

Acta Med Austriaca; 8(3):85-87 1981

A monoclonal marker for hematologic and oncologic purposes was developed. Male BALB/c mice were immunized sc with 4.5 x 10(6) human lymphocytes and boosted ip at monthly intervals with 2-5 x 10(6) of the same type cells. Four days after the last booster dose, spleen cells were obtained from the mice and fused with NS-1 plasmacytoma cells. Polyethylene glycol (40% soln) was used as a fusing agent. Cells were grown on selective heterophilic antibody titer medium. Cells were selected and cloned on the basis of antibody production. Clones were tested for antibody activity against infantile thymus, lymph node, tonsil, bone marrow, and various solid tumor tissues, as well as leukemic and erythroleukemic cells. One IgG 1-producing clone was identified that reacted with lymphoid cells, band cells, polymorphs, eosinophils, and macrophages. The clone did not react with erythropoietic cells or with undifferentiated carcinoma cells. It was designated H Le D 1. Use of this clone allows differential diagnosis of undifferentiated carcinomas and lymphoid malignancies. (10 Refs) (In GER)

20. MONOCLONAL ANTIBODIES: APPLICATION OF B-CELL HYBRIDOMAS TO BIOCHEMICAL RESEARCH.

Tanaka S
Dept. Pathology, Stanford Univ. Sch. Medicine, Stanford, CA, 94305
Tanpakushitsu Kakusan Koso; 26(8):965-976 1981

Protocols for producing B-cell hybridomas (myeloma and plasmacytoma) and antibody-producing cells, steps in screening antibody-producing cells, characteristics of monoclonal antibodies, and biochemical applications of monoclonal antibodies were discussed. Purification of specific antigens and antibodies with the aid of monoclonal antibodies was thought to have potential applications in chemotherapy against specific cancers by means of administration of specific antibodies in the form of monoclonal antibodies. (17 Refs) (In JPN)

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* U. S. GOVERNMENT PRINTING OFFICE: 1982—361-847/110

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CLINICAL EVALUATION AND TREATMENT OF MULTIPLE MYELOMA AND OTHER GAMMOPATHIES

SERIES CT13 No. 82/03

MARCH, 1982

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DIAGNOSIS

1. PSEUDOHYPONATREMIA IN MULTIPLE MYELOMA: A METHOD DEPENDENT ARTIFACT (MEETING ABSTRACT).

Ladenson JH, Koch D
Division Laboratory Medicine, Department of Pathology and Medicine, Washington University School Medicine, St. Louis, MO, 63110
Clin Chem; 27(6):1094 1981

Pseudohyponatremia in patients with multiple myeloma is presumably due to a decrease in plasma water due to the high protein values found in these patients. The decrease in plasma water then leads to low sodium values measured by flame photometry since less sodium is contained in the aliquot of sample taken for analysis. Direct potentiometric analysis of sodium should not be subject to these errors. This was investigated by measuring sodium by direct potentiometry with a Nova-1 analyzer (electrode) and by flame photometry with the Beckman Klina flame photometer (flame) in 53 samples from 24 patients with paraproteins. Differences as large as 17 mMol/L were found. Total protein, water content, osmolality, glucose and urea were also measured. The ratio of flame to electrode

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values decreased as total protein increased but could not be predicted by knowledge of the total protein value. Comparing the ratio with water content also did not allow prediction of the electrode values from the flame values. For electrode values there was no correlation of delta OSMO (measured osmolality value-predicted value) with total protein or water content and delta OSMO av 0.1. However, when flame values were used, the delta OSMO decreased with increasing total protein or decreasing water content and av-11.2. Our data indicate that 1) flame values for sodium are often lower than electrode values in paraproteinemia, 2) the flame and electrode values cannot be interconverted by knowledge of total protein or water content and 3) the electrode sodium values give predicted osmolality values in agreement with those measured but the flame values do not. (no Refs)

2. PARAPROTEINAEMIA: USE OF IDIOTYPIC DETERMINANTS AS SPECIFIC MARKERS FOR TUMOUR ACTIVITY.

King MA, Wells JV
Kolling Inst. Medical Res., Royal North Shore Hosp., St. Leonards NSW 2065, Australia
Clin Exp Immunol; 45(3):544-551 1981

Five patients with paraproteinemia were investigated using anti-idiotype antibodies specific for their paraproteins. Sensitive assays were used to detect soluble paraprotein either in serum or in supernatants from cultures of peripheral blood mononuclear cells (PBMC) and bone marrow cells. It was found that: (i) measurement of serum paraprotein by specific radioimmunoassay is a sensitive method of monitoring the course of multiple and solitary myeloma, (ii) morphologically normal bone marrow from a multiple myeloma patient contained paraprotein-secreting plasma cells, (iii) a patient with benign monoclonal gammopathy had at least one stage in her disease where pre-plasmacytic tumor cells were present in the peripheral blood, (iv) the PBMC of the patients with active myeloma contained suppressor monocytes, and (v) PBMC from treated myeloma patients (both those with still active disease and those in apparently complete remission) would not secrete paraprotein in culture under a variety of different culture conditions including partial monocyte depletion. (Author abstract) (14 Refs)

3. USEFULNESS OF PLASMA CELL ACID PHOSPHATASE IN THE DIFFERENTIAL DIAGNOSIS OF MONOCLONAL GAMMOPATHY.

Santus G, Pirali F, Inzoli MR
Divisione di Medicina Lungodegenza Riabilitazione, Ospedale Generale di Zona 'S. Orsola' Fatebenefratelli, Via V. Emanuele II, 27, 25100 Brescia, Italy
Minerva Med; 72(37):2479-2483 1981

A cytochemical method for differential diagnosis of gammopathy is evaluated. Bone marrow plasma cells from 12 multiple myeloma patients diagnosed by radiology and morphology of sternal puncture, 15 patients with non-myeloma plasmacytosis observed for 1 yr without myelomatous degeneration, and 15 normal controls were analyzed for acid phosphatase activity (AP). Multiple myeloma patients (46-86 yr old) exhibited leukocyte values (LV) of 4,400-8,800 (av 5,900)/ul, Hb 10.2-11.2 g/deciliter (dl), plasma cellular AP of 110-296 unit, and 10-70% bone marrow plasma cells (BMPC). Non-myeloma plasmacytosis patients (47-80 yr old) had LV of 2,800-21,100 (av 7,400)/ul, Hb 7.4-15.2 g/dl, plasma cellular AP of 30-130 unit, and 5-20% BMPC. Normal controls had plasma cellular AP values of 30-120 unit. Use of the plasma cellular AP test is proposed for diagnosis of multiple myeloma. (13 Refs) (In ITA)

CLINICAL IMMUNOLOGY AND IMMUNOTHERAPY

4. CLINICAL SIGNIFICANCE OF IMMUNOGLOBULIN-SECRETING CELLS IN THE PERIPHERAL BLOOD IN PATIENTS WITH MULTIPLE MYELOMA.

Nagai K, Takatsuki K, Uchino H
First Div., Dept. Internal Medicine, Kyoto Univ., 54-Shogoin-Kawaramachi, Sakyo, Kyoto, 606, Japan
Scand J Immunol; 14(2):99-108 1981

Ig-secreting cells were enumerated in the peripheral blood of 31 patients with multiple myeloma, 9 patients with so-called benign monoclonal gammopathy, and 10 patients with polyclonal hypergammaglobulinemia or idiopathic hypogammaglobulinemia. Ig-secreting cells were detected by a hemolytic plaque assay using protein-A-coated RBC in the presence of class- or type-specific rabbit anti-human Ig antisera. In about two-thirds of patients with multiple myeloma cells secreting the same light-chain isotype of their serum M-protein increased in number, whereas this was not the case in the patients with so-called benign monoclonal gammopathy. Follow-up studies of Ig-secreting cells in multiple myeloma revealed that these cells increased or decreased, correlating with the severity of the disease, and alterations were more rapid than other clinical features. This plaque assay is therefore useful in evaluating the response to chemotherapy in patients with multiple myeloma. (Author abstract) (24 Refs)

5. ALTERATIONS OF PERIPHERAL BLOOD B-LYMPHOCYTE POPULATIONS IN PLASMA CELL DISORDERS.

Dillman RO, Royston I, Meserve BL, Griffiths JC
Div. Hematology/Oncology V111E, Veterans Admin. Medical Center, San Diego, CA, 92161
Cancer; 48(10):2211-2217 1981

Peripheral blood lymphocytes of patients with multiple myeloma, macroglobulinemia, and monoclonal gammopathy of uncertain significance were analyzed for B cells, and cells bearing kappa light chains and lambda light chains on their surfaces. Compared with controls, the number of B cells were decreased in all three groups. Contrary to other reports, the authors found a B-cell depression of similar magnitude in patients with untreated myeloma and in those with apparently benign monoclonal gammopathy. There was no difference between treated and untreated myeloma patients as a group, or as individuals studied before and after treatment. However, in comparison to control patients, alkylator therapy depressed the WBC count, lymphocyte count, and B-cell number both in the myeloma and in the macroglobulinemia groups. All five patients with previously untreated macroglobulinemia had an increased proportion of circulating lymphocytes with surface light chains of the same type as the M protein. Two patients with IgG myeloma-like disorders had increased circulating B cells with monoclonal surface light chains. This study supports the concepts that normal B cells are depressed in plasma cell disorders, and that abnormal B cells, which are apparently monoclonal, do circulate in some cases. Our results are compared with other published data. (Author abstract) (38 Refs)

6. CELL-BOUND IMMUNOGLOBULIN ON PERIPHERAL BLOOD MONONUCLEAR CELLS OF PATIENTS WITH MYELOMA.

King MA, Wells JV
Kolling Inst. Medical Res., Royal North Shore Hosp. Sydney, St. Leonards, 2065 NSW, Australia
Clin Exp Immunol; 45(3):552-556 1981

Four patients who had myeloma were examined for monoclonal lymphocytes in the peripheral blood using anti-idiotype antibodies. All the patients had received treatment and two were in apparent complete remission. In no case was there any evidence of peripheral blood mononuclear cells (PBMC) with endogenous surface idiotypic determinants, even in patients with active disease. It was found, however, that substantial cytophilic IgG may remain bound to Fc receptors on PBMC even after extensive incubation and washing at 37 C. (Author abstract) (19 Refs)

7. PWM-INDUCED GENERATION OF IMMUNOGLOBULIN-SECRETING CELLS IN PATIENTS WITH MULTIPLE MYELOMA.

Sieber G, Enders B, Ruhl H
Hamatologische Abteilung, Klinikum Steglitz der FU, Hindenburgdamm 30, D-1000 Berlin 45, W. Germany
Klin Wochenschr; 59(19):1101-1108 1981

The pokeweed-mitogen-induced transformation of B-lymphocytes into Ig-secreting cells was studied in vitro in 25 patients with multiple myeloma using a reverse hemolytic plaque assay. Fifteen patients showed a good response in generating Ig-secreting cells, whereas 10 patients showed a decreased B cell reactivity which was not due to intermittent melphalan/steroid therapy administered to 15 patients. Experiments with lymphocyte subpopulations demonstrated that the inability of some multiple-myeloma patients to generate Ig-secreting cells was always based on a defect in the B-cell subset. Co-culture experiments with lymphocytes from normal individuals and patients revealed a cell-mediated suppression in one case, where as humoral suppressive factors in the patients' serum could not be observed using the reverse hemolytic plaque assay. Patients were classified into three groups: (a) patients with a normal B-cell function, (b) patients with a reversible, tumor-dependent suppression of B-cell reactivity and (c) patients in whom the normal B-cell population was replaced by non-reactive cells. (Author abstract) (52 Refs)

8. A PHASE I STUDY OF HUMAN LYMPHOBLASTOID INTERFERON IN PATIENTS WITH HEMATOLOGICAL MALIGNANCIES.

Rohatiner A, Balkwill F, Malpas JS, Lister TA
Dept. Medical Oncology, St. Bartholomew's Hosp., West Smithfield, London EC1A 7BE, England
Haematol Blood Transfus; 26:63-67 1981

Preliminary results of a Phase I study of human lymphoblastoid interferon (HLBI) in patients with acute myeloblastic leukemia (AML: 10), follicular non-Hodgkin's lymphoma (1), myeloma (1), and chronic lymphocytic leukemia (1) are described. All patients complained of general malaise and anorexia, and became pyrexial between 2 and 24 hr after administration of HLBI. Of the 13 patients, 4 complained of rigors, 3 of headaches, and 1 of joint pains. One patient experienced a hypotensive episode after the second injection of HLBI. All patients had bone marrow infiltration rendering interpretation of the blood count extremely difficult. In patients with AML, a fall in Hb and platelet counts was compatible with advancing disease. No evidence of renal impairment was found; liver function tests remained normal. Serum interferon activity was measured. The results indicated that up to 10 x 10(6) unit/square meter iv can be given daily; to avoid toxicity and achieve consistent levels, iv HLBI should be given by continuous infusion. After iv injection of HLBI, high peak levels were achieved at 30 min, but interferon was rapidly cleared in the first hr after injection. When given by continuous iv infusion, interferon levels increased over 72 hr and then remained elevated. Results of the in vitro study confirmed the cell growth inhibitory effects of HLBI on human myeloblasts. The degree of growth inhibition was dose dependent. However, the concentration of interferon that resulted in 50% inhibition of growth in vitro was 3-10x higher than the serum levels attained. (7 Refs)

RADIOTHERAPY

9. HALF BODY IRRADIATION FOR TREATMENT OF METASTATIC PROSTATIC CARCINOMA AND PLASMA CELL MYELOMA (MEETING ABSTRACT).

Rowland CG
Radiotherapy Centre, Bristol Royal Infirmary, Bristol, England
Br J Radiol; 54(640):372 1981

High-dose radiation therapy as a single fraction to the upper and lower halves of the body provides effective palliation of widespread malignant disease, particularly in tumors believed to have a slow doubling time such as prostate, gut and myeloma. Some 100 patients are treated each yr by this meth od in Bristol at the present time. The radiation is delivered by an 8 MeV linear accelerator at 200 cm SSD, with a tissue max of 750 centiGray (cGy) (rad) given to the upper half of the body and 1000 cGy to the lower half the two treatments being spaced one mo apart to allow bone-marrow recovery in the untreated half. A pretreatment infusion of 500 ml normal saline containing 20 ml potassium and 100 mg hydro-cortisone is given before each treatment. This appears to be effective in limiting the immediate effects of radiation sickness. Another short-term side effect is swelling of the salivary gland, which resolves spontaneously within one to two days. Long-term complications include epilation and xerostomia which revert to normal after about six mo. In a separate study, five patients with plasma-cell myeloma and high tumor-cell mass have been treated by halfbody irradiation. Three patients are alive at 25, 24 and 24 mo. The percentage of plasma cells in the upper and lower half of the body and the plasma immunoglobulins have been significantly reduced at six mo. This study clearly shows that single doses of radiation reduce the number of tumor cells by a factor of about 100 in humans. (no Refs)

SELECTED PRE-CLINICAL STUDIES

10. BENIGN MONOCLONAL GAMMOPATHY (IDIOPATHIC PARAPROTEINEMIA).

Radl J
Inst. for Experimental Gerontology, Organization for Health Res. TNO, P.O. Box 5815, 2280 HV Rijswijk, The Netherlands
Am J Pathol; 105(1):91-93 1981

Studies of benign idiopathic paraproteinemia (IP) in aging C57BL mice showed that the major features of this disease are the same as those of human IP. Such studies should increase the understanding of the causes and pathogenesis of IP in humans, the relationship between benign and malignant disorders of the immune system, and the changes that appear within the system as a consequence of aging. (12 Refs)

11. MYELOMA PROTEIN WITH THREE LIGHT CHAINS (MEETING ABSTRACT).

Sun T, Lien YY, Erikson RB, Wu CH
North Shore University Hospital, Cornell University Medical College, Manhasset, NY, 11030
Clin Chem; 27(6):1065 1981

Bence Jones proteinemia is relatively uncommon as compared to Bence Jones proteinuria in myeloma patients. The former has always been demonstrated as one single monoclonal free light chain in serum. We report here an unusual case in which 3 light chains were detected in the serum including 1 bound to IgG and 2 others free. The diagnosis of myeloma in this 53 yr-old man was established by the presence of atypical plasma cells in the bone marrow which showed myelofibrosis, and the radiologic finding of multiple osteolytic bone lesions. The patient also manifested hypercalcemia, poor renal function and an unusual initial clinical presentation of congestive heart failure. Electrophoresis showed a prominent cathodal IgG-kap pa band and 2 kappa light chain bands in beta region. The components of these bands were identified by immunoelectrophoresis and immunofixation. IgG was 1945 mg/dl (normal 800-1800), IgA 120 mg/dl (normal 90-450) and IgM less than 20 mg/dl (normal 60-250). One free light chain only was seen in the urine. The mol wt of the 2 free light chains as determined by sodium dodecyl sulfate-polyacrylamide gel electrophoresis were 52,000 (dimer) and 25,000 (monomer). It is postulated that the presence of 2 free light chains were due to unbalanced synthesis and incomplete dimerization of immunoglobulins in myeloma cells. (no Refs)

12. CALCIUM BINDING BY AN IGG MYELOMA PROTEIN (MEETING ABSTRACT).

Annesley T, Kyle R, Burritt M
Department of Laboratory Medicine, Mayo Clinic, Rochester, MN, 55901
Clin Chem; 27(6):1096 1981

Hypercalcemia occurs in one-third of patients with multiple myeloma. This requires immediate treatment because renal failure often develops. In rare individuals, hypercalcemia is asymptomatic and the ionized calcium is normal because of binding with the monoclonal protein. We have isolated and characterized a monoclonal protein capable of binding calcium. Three preparations of this IgG kappa myeloma protein bound 45 calcium in amounts proportionate to the protein concentration. Digestion using papain yielded FAB and FC fragments. Only the FAB fragment bound 45 calcium in amounts comparable to the intact IgG molecule. Neither purified heavy or light chains possessed calcium binding activity. However, reconstitution of the heavy and light chains yielded an IgG molecule capable of calcium binding. In testing for multiple ion binding by this IgG kappa protein, there was no observed ability to bind magnesium. Analysis of this protein compared with 17 control myeloma proteins, by two-dimensional electrophoresis, revealed and unusually acidic light chain in the calcium binding myeloma protein. The acidic property is one shared with other cation binding proteins, including myeloma proteins, coagulation factors, and calcium binding glycoproteins. Our data suggests that a specific three-dimensional conformation of negative charges is required for calcium binding to occur. (no Refs)

13. THE MODE OF ACTION OF SPLENIC SUPPRESSOR CELLS IN MURINE PLASMACYTOMA.

Chen Y, Heller P
Veterans Admin. West Side Medical Center, PO Box 8195, Chicago, IL, 60680
Clin Exp Immunol; 45(3):514-522 1981

Polyclonal IgM secretion after LPS stimulation and antigen-dependent antibody production by splenic cells of BALB/c mice with plasmacytoma were found to be markedly reduced. The former occurred without mediation of suppressor cells, probably as the result of a quantitative reduction of mitogen-responsive B lymphocytes. On the other hand, the reduction in the generation of antibodies to sheep RBC in vi tro, as determined by the number of PFC, was found to be dependent on the activity of suppressor cells which had the functional characteristics of macrophages. The targets of these suppressor cells were found to be normal macrophages, B and T lymphocytes which were all independently suppressed. A diffusible factor appeared to be responsible for the suppressive effect of the suppressor macrophages interfering mainly with those early stages of the immune response involving antigen-triggered B cell activation. (Author abstract) (30 Refs)

14. PRACTICAL APPLICATIONS OF MONOCLONAL ANTIBODIES AGAINST CARCINOEMBRYONIC ANTIGEN (CEA) (MEETING ABSTRACT).

Mach JP, Buchegger F, Phan M, Forni M, Ritschard F, Accolla R, Carrel S
Ludwig Institute for Cancer Research, Lausanne Branch, 1066 Epalinges, Switzerland
Ve Colloque International de Radioimmunologie de Lyon, April 9-11, 1981, Lyon, France. Centre de Medecine Nucleaire 101 pp., 1981.

Monoclonal antibodies against CEA produced by hybrid cells derived from fusion between spleen cells from mice immunized with purified CEA and cells from the P3-NSI/1-Ag4 myeloma were purified from hybridoma ascites by ammonium sulfate precipitation and DE-52 chromatography. The purified antibodies which had been shown to have a high specificity and affinity for CEA were tested for two major practical applications. First, they were used to develop a solid-phase enzymeimmunoassay capable of detecting 0.6-1.2 ng per ml of patient serum which proved as efficient as the presently available radio- and enzymeimmunoassay. Second, they were labelled with 131I and injected into tumor bearing patients in order to study the tumor localization of the antibodies. The results from these pilot studies, obtained by external scanning of the patients and by direct measurement of the radioactivity in resected tumors and adjacent normal tissues, showed that monoclonal anti-CEA antibodies are capable of specific tumor localization in some patients. Ten out of 20 patients with colon carcinoma injected with labeled monoclonal antibodies showed positive 'immuno-scintigraphy'. The specificity indices of localization

obtained by comparing in fragments of tumor and normal tissues, the 131I radioactivity of the antibodies with the 125I radioactivity of control normal mouse IgG injected simultaneously with the antibodies, gave values ranging from 2-5. These encouraging results, however, are not sufficient to recommend this method of immuno-scintigraphy for routine tumor detection. (no Refs)

15. MONOCLONAL ANTIBODIES TO DIFFERENTIATION ANTIGENS OF NORMAL HUMAN MAMMARY EPITHELIAL CELLS (MEETING ABSTRACT).

Peterson JA, Moncada FR, Cerianai RL

Bruce Lyon Memorial Research Laboratory, Children's Hospital Medical, Center 51st and Grove Streets, Oakland, CA, 94609

In Vitro; 17(3):225 1981

Hybridomas were prepared that secrete monoclonal antibodies to surface antigens of normal human mammary epithelial (HME) cells by fusion of mouse myeloma cells with spleen cells from BALB/c mice immunized with human milk fat globule (HMFG) membranes. Preliminary selection for presumptive breast specificity was based on specific binding to HMFG membranes and not to membranes from human mammary fibroblasts, or HeLa, HT-29, or lymphoblastic cell lines. Specificity of binding to HME cells was shown by competion with solubilized HMFG and with rabbit anti-HME antisera. Five different hybridomas have been prepared, all of which bind to surface antigens of normal HME cells while each binds differently to several human breast carcinoma cell lines, thus indicating a heterogeneity in surface antigens of breast tumors. We have previously shown that the HMFG membrane is made up of four major components, three of which contain antigens specific for HME cells. The monoclonal antibodies bind to at least two different mol wt components. These hybridomas will be useful in characterizing surface antigens of normal HME cells and in classifying breast tumors. (1 Ref)

16. DEVELOPMENT OF A MONOCLONAL ANTIBODY AGAINST A TUMOR-ASSOCIATED ANTIGEN (MEETING ABSTRACT).

Peng WW, Bressler JP, Tiffany-Castiglioni E, De Vellis J, Hail W

University of California Los Angeles, Los Angeles, CA, 90024

In Vitro; 17(3):225 1981

A monoclonal antibody-producing hybrid cell line has been obtained by fusing mouse myeloma cells with spleen cells from a mouse previously immunized with C6 rat glioma cells. The antibody was determined to be IgG by immunofluorescence microscopy. Cell surface binding studies with 125I-protein A indicated that this antibody recognizes C6 rat glioma cells, rat B104 neuroblastoma cells, and spontaneously or chemically transformed oligodendrocytes and astrocytes. It also binds to human glial tumor cells. On the other hand, it does not recognize (a) normal rat cell lines of skin fibroblasts or astrocytes, and (b) primary cultures of oligodendrocytes or astrocytes. A weak binding of this antibody occurred on two rodent hepatoma cell lines, H-4-II-E-C3 and Hepa 1, as well as on primary rat hepatocyte cultures. Direct tissue binding experiments indicated that this antibody does not bind to normal rat brain tissue, although some binding to liver cells is observed. We conclude that this antibody binds to a specific cell surface antigen which is absent on normal brain tissues but is present on all the rat and human neural tumor cell lines studied. (no Refs)

17. MONOCLONAL ANTIBODIES TO HUMAN PROSTATE AND BLADDER TUMOR ASSOCIATED ANTIGENS (MEETING ABSTRACT).

Starling JJ, Sieg SM, Wright GL

Eastern Virginia Medical School, P.O. Box 1980, Norfolk, VA, 23501

In Vitro; 17(3):224 1981

Monoclonal antibodies to human prostate adenocarcinoma membrane antigens were produced by fusion of spleen cells from BALB/c mice immunized against the prostate adenocarcinoma cell line, DU145, and the P3-X63-Ag8 (P3) myeloma line or the non-secreting 653 variant of the P3 line. The hybrids were screened for antibody production using a solid-phase in vitro binding radioimmunoassy (RIA). Some hybrids produced antibody specific for the immunizing tumor cells and others produced antibody cross-reactive against several tumors, but not normal cell lines. One of these hybrid lines (DU83.21) secreted antibody that preferentially bound to prostate tumor cells and bladder tumor cells and exhibited weak or no binding to 40 other tumor and normal cell lines tested by RIA. Conventional and competitive binding studies suggest the DU83.21 antibodies do not bind to alpha-fetoprotein, carcinoembryonic antigen, prostatic acid phosphatase, HLA, or DR antigens. Biochemical characterization of the prostate adenocarcinoma membrane antigens is in progress and will be accomplished by immunoprecipitating detergent soluble 125I-labeled cell surface antigens with the DU83.21 monoclonal antibodies followed by sodium dodecyl sulfate gel electrophoresis and autoradiography. (no Refs)

18. EXPRESSION OF MYELOID DIFFERENTIATION ANTIGENS ON NORMAL AND MALIGNANT MYELOID CELLS.

Griffin JD, Ritz J, Nadler LM, Schlossman SF

Div. Tumor Immunology, Sidney Farber Cancer Inst., Harvard Medical Sch., Boston, MA, 02115

J Clin Invest; 68(4):932-941 1981

A series of monoclonal antibodies have been characterized that define four surface antigens (MY3, MY4, MY7, and MY8) of human myeloid cells. They were derived from a fusion of the NS-1 plasmacytoma cell line with splenocytes from a mouse immunized with human acute myelomonocytic leukemia cells. MY3 and MY4 are expressed by normal monocytes and by greater than 90% of patients with acute monocytic leukemia or acute myelomonocytic leukemia, but are detected much less often on other types of myeloid leukemia. MY7 is expressed by granulocytes, monocytes, and 5% of normal bone marrow cells. Seventy nine percent of all acute myeloblastic leukemia (AML) patients tested (72 patients) express MY7 without preferential expression by any AML subtype. MY8 is expressed by normal monocytes, granulocytes, all peroxidase-positive bone marrow cells, and 50% of AML patients. MY3, MY4, and MY8 define myeloid differentiation antigens in that they are not detected on myeloid precursor cells and appear at discrete stages of differentiation. These antigens are not expressed by lymphocytes, RBC, platelets, or lymphoid malignancies. The monoclonal antisera defining these antigens have been used to study differentiation of normal myeloid cells and malignant myeloid cell lines. (Author abstract) (49 Refs)

REVIEWS

19. MONOCLONAL ANTIBODIES: THE NEXT ATTEMPT AT TUMOR IMMUNOTHERAPY.

Boman BM, Fathman CG
Mayo Graduate Sch. Medicine, Rochester, MN
Mayo Clin Proc; 56(10):641-644 1981

Production of monoclonal antibodies (MAs) and their potential applications in cancer immunotherapy are discussed. The MAs are obtained by the fusion of mouse myeloma cells with splenocytes from mice immunized with tumor cells. Cells secreting the desired tumor antibody can be cloned by limiting dilution and maintained in culture indefinitely. Once MAs specific for tumor antigens have been identified, recombinant genetic engineering might be used to obtain bacteria that produce the antibody variable region containing the tumor antigen binding site. Conjugates of chemotherapeutic agents, radioisotopes, or plant toxins and MAs may provide the specificity needed for effective in vivo antitumor activity. Pharmacokinetic factors that influence the efficacy of antibody therapy are summarized. (21 Refs)

* U. S. GOVERNMENT PRINTING OFFICE : 1982—361-847/112

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CLINICAL EVALUATION AND TREATMENT OF MULTIPLE MYELOMA AND OTHER GAMMOPATHIES

SERIES CT13 No. 82/04

APRIL, 1982

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DIAGNOSIS

1. RELATIONSHIP BETWEEN SERUM VISCOSITY AND INTRAVASCULAR IGA POLYMER CONCENTRATION IN IGA MYELOMA.

Chandy KG, Stockley RA, Leonard RC, Crockson RA, Burnett D, Maclennan IC
Immunodiagnostic Res. Lab., Univ. Birmingham Medical Sch., Birmingham B15 2TJ, England
Clin Exp Immunol; 46(3):653-661 1981

Thin-layer chromatography followed by crossed immunoelectrophoresis was used to examine the relationship between serum viscosity and IgA polymer concentration in 33/179 IgA myeloma patients. The range of relative serum viscosity (RSV) for serum from healthy donors was 1.25-1.7. An RSV of greater than 1.7 was observed in 149/179 of the myeloma patients. The RSV of the 33 patients examined further ranged from 1.31-5.88 with two patients having RSV of 9.51 and 9.76. The proportion of IgA polymer in the 33 patients ranged from 0-88%. The correlations between RSV and serum monomer equivalent IgA concentration (rs = 0.3091, p greater than 0.05), and RSV and actual IgA monomer concentration (rs = 0.0024, p greater than 0.1) were poor. A strong correla-

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tion was observed between RSV and the serum IgA polymer equivalent concentration (rs = 0.7928, p less than 0.001). On serial dilution of sera from 4/31 patients without marked hyperviscosity, the relative serum viscosity was observed to decrease rapidly at first and then more gradually. The two hyperviscous sera exhibited a more marked initial reduction in RSV. The RSV was higher at 23 C than at 37 C in the sera of 7/31 patients without marked hyperviscosity. The same temperature change resulted in a far greater increase in RSV in the two markedly hyperviscous sera. IgA polymers, larger than dimers, were demonstrated in 7/33 sera; none were observed in the sera of two patients with markedly hyperviscous sera. The serum hyperviscosity did not seem to be dependent on the presence if IgA polymers larger than dimers. IgA complexes with albumin, beta-1-lipoprotein, and alpha-1-antitrypsin were observed in some sera with lower RSV. However, IgA complexes with these plasma proteins were not detected in the two markedly hyperviscous sera. Protein aggregation seemed to be a major determinant in the development of serum hyperviscosity in the two patients with marked hyperviscosity. (22 Refs)

2. IMMUNOPEROXIDASE STAINING OF BONE MARROW SECTIONS.

Hitzman JL, Li CY, Kyle RA
(c/o Li) Dept. Lab. Medicine, Mayo Clinic, Rochester, MN, 55905
Cancer; 48(11):2438-2446 1981

Paraffin-embedded sections of bone marrow from 131 patients were studied. The specificity of the immunoperoxidase technique for detecting intracellular kappa and lambda light chains of Ig was first evaluated in 34 cases of typical multiple myeloma or macroglobulinemia. The monoclonal light chain detected in the bone marrow myeloma cell was identical to the result of immunoelectrophoresis of serum or urine. By use of the same method, 97 cases in which the diagnosis was difficult were examined; cases included those of bone marrow plasmacytosis, lymphocytosis, and morphologically unusual cells. All marrow cells with monoclonal Ig detected by immunoperoxidase stain eventually proved to be a B-cell neoplastic or potentially neoplastic process. This study confirms the specificity of the immunoperoxidase stain and demonstrates its value in solving clinical diagnostic problems, that is, the diagnosis of nonsecretory myeloma and myeloma with unusual morphology, differentiating the monoclonal plasmaproliferative disorders from reactive plasmacytosis or lymphoma from lymphocytosis. (Author abstract) (23 Refs)

3. SPONTANEOUS IMMUNOGLOBULIN CHANGES IN HUMAN PLASMA-CELL DYSCRASIA.

Carter A, Spira G, Manaster J, Tatarsky I
(c/o Spira) Faculty Medicine, Technion, P.O. Box 9649, Haifa, Israel
Scand J Haematol; 27(2):111-118 1981

A series of spontaneous changes affecting the nature of the immunoglobulin secretion of plasma cells is described in a patient initially diagnosed as IgG lambda benign monoclonal gammopathy. After several years a slight increase in the amount of serum monoclonal immunoglobulin occurred; shortly thereafter an aggressive form of multiple myeloma was diagnosed. Unexpectedly a rapid spontaneous decrease of the monoclonal immunoglobulin, accompanied by the appearance in the serum of increasing quantities of a complex containing intact lambda light chains, then occurred. Concomitantly a fragment of the corresponding free light chain was detected in the urine. A parallel is drawn between the facts observed in this patient and in an animal model recently proposed to explain the different types of structural immunoglobulin abnormalities in multiple myeloma. (Author abstract) (11 Refs)

CLINICAL IMMUNOLOGY AND IMMUNOTHERAPY

4. LEUKOCYTE INTERFERON-INDUCED TUMOR REGRESSION IN HUMAN METASTATIC MALIGNANT DISEASE RESISTANT TO CHEMOTHERAPY (MEETING ABSTRACT).

Medenica R, Emodi G, Miescher PA
Department of Medicine, University Hospital Geneva, Geneva, Switzerland
Twelfth International Congress of Chemotherapy, July 19-24, 1981, Florence, Italy. The International Society of Chemotherapy 301 pp., 1981.

A phase II study with partially purified WBC interferon obtained by Cantell technique, modified by Soos (using Cantell strain Sendai virus) has been carried out in 42 patients with advanced cancer (breast, lung adenocarcinoma, gastric, prostatic, melanoma and multiple myeloma. Patients were treated by im injections of 3 x 10(6) IU/m2, in periods of 3 to 5 days every 2 wk during 6 mo. Complete clinical response was obtained in the following cases: cancer of breast: 1 out of 9, prostata: 1 out of 6, melanoma: 1 out of 6, multiple myeloma: 2 out of 6 cases. Tumor regression was observed in the following cases: cancer of breast: 4 out of 8, lung: 4 out of 8, stomach: 4 out of 7, prostata: 3 out of 6, melanoma: 2 out of 6, multiple myeloma: 3 out of 6 cases. Circulating interferon level 4 hr after the injection was in the range of 30 to 50 IU/ml of plasma. Side effects included febrile reactions (usually 2-4 hr after injection), malaise and asthenia to a varying degree. In one patient reversible thrombopenia (60,000) and leukopenia (2,200) were observed. No side effects were observed with regard to cardiac, renal and hepatic functions, which were carefully monitored. (no Refs)

5. T-CELL SUBPOPULATIONS IN MULTIPLE MYELOMA: CORRELATION WITH CLINICAL DISEASE STATUS.

Oken MM, Kay NE
Hematology Section (111E), Veterans Admin. Medical Center, 54th St. and 48th Ave. S., Minneapolis, MN, 55417
Br J Haematol; 49(4):629-634 1981

T-lymphocyte subpopulations bearing Fc receptors for IgM (Tmu) or for IgG (Tgamma) were studied in blood specimens obtained from 40 normal volunteers and from 16 patients with multiple myeloma. The myeloma patients showed a significant imbalance in T-cell subpopulations characterized by an increase in the percentages of Tgamma cells to 30.0 +-3.9% (mean +- SEM) compared with 12.0 +-3.0% for the controls (p less than 0.001). The patients exhibited a decreased proportion of Tmu cells (13.4 +-4.1%) compared with the control value of 55 +-7% (p less than 0.001). When the results were analyzed according to clinical status it was the patients with indolent or well-controled disease and not those with progressive disease who exhibited an elevated proportion of Tgamma cells. The elevation of Tgamma cells or of a subpopulation of suppressor cells should be further studied as a possible mechanism of disease control in multiple myeloma. (Author abstract) (19 Refs)

6. CLINICAL AND IMMUNOCHEMICAL STUDIES OF 20 PATIENTS WITH AMYLOIDOSIS AND PLASMA CELL DYSCRASIA.

Pick AI, Frohlichmann R, Lavie G, Duczyminer M, Skvaril F
Section Clinical Immunology, Beilinson Medical Center Tel Aviv Univ., Medical Sch., Petah Tikva, Israel
Acta Haematol (Basel); 66(3):154-167 1981

Amyloidosis associated with plasma cell dyscrasia (AAPCD) is a relatively rare clinical entity (4% of our patients with PCD) and its early recognition and distinction from multiple myeloma (MM) may be of great therapeutic and prognostic significance. Laboratory parameters, such as concentrations of normal polyclonal Ig, Bence-Jones proteins and serum monoclonal components (MC) showed in our patients lower MC concentrations than in MM, lambda-L-chains and of gamma-H-chains predominating. Sequential skeletal x-ray studies and bone marrow morphology remain essential diagnostic procedures. Due to the lack of efficient therapeutic agents for AAPCD and the great progress achieved in recent yr in the treatment of secondary amyloidosis, the immunochemical analysis of the isolated amyloid fibril as well as of the surrounding 'ground substance' should be pursued in AAPCD. Our data support previous observations, that in AAPCD the amyloid fibril subunit is an L-chain fragment predominantly derived from lambda-L-chains which originates from the same clone as the MC. The localization of an enzymatic cleavage point on the L-chain, the detection of a specific proteolytic enzyme and the identification of additional components in the amyloid substance, may further elucidate the etiopathogenesis of AAPCD. (Author abstract) (39 Refs)

7. PHASE II TRIAL OF HUMAN FIBROBLASTIC INTERFERON IN MALIGNANT GAMMAPATHIES AND MENINGEAL LEUKEMIA (MEETING ABSTRACT).

Misset JL, Gastiaburu J, Goutner A, De Vassal F, Mathe G
ICIG, Inserm U-50, Hospital Paul-Brousse, 94800-Villejuif, France
Twelfth International Congress of Chemotherapy, July 19-24, 1981, Florence, Italy. The International Society of Chemotherapy 301 pp., 1981.

Eighteen patients (16 myelomas and 2 Waldenstrom's disease) were submitted to a phase II trial of human fibroblastic interferon (RPMI) given iv: 6 million units weekly (Group A: 7 patients) or 3 million units twice weekly (group B: 11 patients). Three patients stopped treatment after 3.3 and 15 infusions for major side effects. Other side-effects were minor and more pronounced in group A. Reduction in M component greater than 50% of initial value was not seen. More than 25 percent was seen in 3 patients. Response became significant only after 3 mo in one patient. Bence Jones proteinuria disappeared in one patient. Bone marrow plasmocytosis decreased greater than 50% in 4 patients and bone pain was significantly decreased in 5 patients. Natural killer (NK) activity studies in these patients did not show clear correlation between level of activity prior or after treatment and response. Patients having meningeal relapse of acute lymphoid leukemia (4 patients) and leukemic lymphosarcoma (1 patient) were given interferon: 1.3 million units daily or qod up to remission or failure. Four patients failed to improve after 5 to 8 injections (and given methotrexate) 1 complete remission was obtained after 11 injections and is still maintained under chemotherapy. Tolerance was good in all cases. NK activity studies were not performed in this five patients. Further studies are warranted in these two clinical situations. (no Refs)

8. INTERFERON THERAPY IN MULTIPLE MYELOMA: FAILURE OF HUMAN FIBROBLAST INTERFERON ADMINISTRATION TO AFFECT THE COURSE OF LIGHT CHAIN DISEASE.

Billiau A, Bloemmen J, Bogaerts M, Claeys H, Van Damme J, De Ley M, De Somer P, Drochmans A, Heremans H, Kriel A, Schetz J, Tricot G, Vermylen C, Verwilghen R, Waer M
Dept. Human Biology, Rega Inst., K. U. Leuven, Minderbroedersstraat 10, B-3000 Leuven, Belgium
Eur J Cancer Clin Oncol; 17(8):875-882 1981

Fibroblast interferon at a dosage of 28 x 106U/wk failed to influence disease progression in a preterminal case of therapy-resistant light chain myeloma. In a second case, that had not previously been treated, a first course of fibroblast interferon (30 x 106U/wk) associated with corticosteroids remained without effect. In this patient subsequent leukocyte interferon treatment was associated with a decrease in urinary light chain excretion and normalization of calcemia, all other parameters remaining unaltered. A third patient with light chain disease was resistant to chemotherapy ab origine. None of the disease parameters responded to either fibroblast or leukocyte interferon therapy (21 x 106U/wk). During therapy a downward trend occurred in the relative number of lymphocytes characterizable as B and T cells. Mitogenic reactivity remained unchanged except for a downward trend, during fibroblast interferon therapy, in reactivity to PHA and Con A after 6 days culturing. Spontaneous (background) mitogenesis upon culture showed an upward trend. (Author abstract) (26 Refs)

CHEMOTHERAPY

9. POLYAMINE (SPERMIDINE) LEVELS AS A MARKER OF EARLY RESPONSE TO THERAPY IN HUMAN MYELOMA (MEETING ABSTRACT).

van Dobbenburgh OA, Jurjens H, Marrink J, Nieweg HO, Houwen B
Div. of Hematology, Dept. of Medicine, University of Groningen, Groningen, The Netherlands
Twelfth International Congress of Chemotherapy, July 19-24, 1981, Florence, Italy. The International Society of Chemotherapy 301 pp., 1981.

Patients with multiple myeloma who were resistant to melphalan-prednisone were treated with vindesine, a new vinca alkaloid. Sixteen patients received vindesine 2 mg/m2 iv. Spermidine levels were recorded at 2 hr intervals on the first day, and for 5-7 consecutive days. Follow up treatment consisted of vindesine weekly for 3 wk combined with oral prednisone. After two cycles treatment response was evaluated by measuring M-component serum level or urinary excretion, Hb concentration, serum calcium level, and changes in osteolytic lesions. In responding patients the plasma spermidine levels were max on day 2 or 3, but changes could be observed within hr after vindesine. In non-responding patients changes were minimal or absent. The spermidine level at 5-7 days was of little prognostic value. It seems therefore that early changes in spermidine plasma level after cytotoxic therapy may be careful as a prognostic marker of response to the therapy in human myeloma. (no Refs)

10. PHASE II STUDY OF CHLOROZOTOCIN IN LEUKEMIA AND OTHER HEMATOLOGIC MALIGNANCIES.

Pavlovsky S, Woolley PV, Garay G, Scaglione C, Hoth D, Schein PS
(c/o Woolley) Div. Medical Oncology, Georgetown Univ. Hosp., 3800 Reservoir Road, NW, Washington, DC, 20007
Cancer Treat Rep; 65(11/12):1109-1111 1981

Chlorozotocin (120 mg/square meter, iv) was administered weekly or daily for 3 days to 20 acute leukemia patients and every 6 wk to 11 lymphoma and myeloma patients. Weekly treatment resulted in some reduction of circulating blast cells in 2/5 patients with acute myelocytic leukemia and in 3/7 with acute lymphocytic leukemia, but no bone marrow responses were noted. Daily treatment for 3 days produced a significant decrease in circulating blast cells in 6/7 patients but no bone marrow response. Thrombocytopenia was the only toxic effect observed in these patients. Objective responses (reduction in cervical adenopathy and in hilar nodes) occurred in 2/5 patients with Hodgkin's disease. No objective responses were obtained in 11 patients with non-Hodgkin's lymphoma or in the 2 multiple myeloma patients. However, one myeloma patient had symptomatic improvement and a 50% decrease in serum paraprotein. Drug toxicity was minimal in this group. (6 Refs)

CASE REPORTS

11. CEREBRAL COMPRESSION BY MYELOMA.

Stark RJ, Henson RA
Neurological Dept., London Hosp., Whitechapel E1 1BB, London, England
J Neurol Neurosurg Psychiatry; 44(9):833-836 1981

A patient presented with right hemiparesis, dysphasia and a large, palpable, left frontoparietal mass arising from the calvarial diploe. A diagnosis of multiple myeloma was made on radiological and biochemical grounds, together with bone marrow examination. Few cases of cerebral compression by a massive plasmacytoma have been reported, but in some surgical management produced clinical deterioration. The present case was treated with radiotherapy and chemotherapy, with satisfactory results. (Author abstract) (24 Refs)

SELECTED REPORTS ON ETIOLOGY AND EPIDEMIOLOGY

12. MULTIPLE MYELOMA IN THE UNITED STATES, 1950-1975.

Blattner WA, Blair A, Mason TJ
Environmental Epidemiology Branch, NCI, Landow Building, Room 4C-18, Bethesda, MD, 20205
Cancer; 48(11):2547-2554 1981

A total of 68,400 whites and 10,533 nonwhites were reported to have died from multiple myeloma (MM) in the continental United States between 1950 and 1975 (excluding 1972 because of incomplete case ascertainment). Age-adjusted mortality rates for nonwhites were approx twice as high as for whites. During the 25-yr period of this survey, there was a twofold to threefold increase in MM mortality. The increase was seen in both races, but was greater in nonwhites than whites and primarily occurred in people over 55 yr of age. The increases were uniform in all geographic regions and urban/rural categories. MM mortality from 1950-1969 was correlated with geographic, demographic, and occupational factors at the county level. The rates were highest in the far west and mid-central regions for whites and in the northeast for nonwhites. Urban areas had the highest rates and rural areas had the lowest, and positive associations were seen with indices of socioeconomic level and the percentage of residents with Scandinavian ancestry. For white males, MM mortality rates were elevated in areas with high petroleum and paper production, and a slight increase was seen in furniture manufacturing areas. (Author abstract) (34 Refs)

SELECTED PRE-CLINICAL STUDIES

13. NUCLEOLAR IMMUNOFLUORESCENCE IN BONE MARROW SPECIMENS OF HUMAN HEMATOLOGICAL MALIGNANCIES.

Smetana K, Busch RK, Hermansky F, Busch H
(c/o H. Busch) Dept. Pharmacology, Baylor Coll. Medicine, Houston, TX, 77030
Blut; 42(2):79-86 1981

Nucleolar immunofluorescence (NIF) produced with HeLa cell nucleoli antibodies was studied in three patients with acute myeloid leukemia (AML), four with chronic myeloid leukemia (CML), five with multiple myeloma (MM), and five with chronic lymphocytic leukemia (CLL: B-cell type). In CML, bright NIF was mainly observed in blastic cells. The percentage of such cells with NIF ranged from 10-80%. The appearance of such cells is described. Other stages of the granulocytic line in CML marrows, such as promyelocytes, myelocytes, and metamyelocytes usually did not contain NIF; in fluorescent cells, the NIF was less bright than in myeloblasts. Other CML bone marrow cells in the same specimens did not exhibit NIF including those identified as erythroblasts and megakaryocytes. In AML, bright NIF was also observed in a variable number of blastic cells whose fluorescent nucleoli resembled those of myeloblasts. The other bone marrow nucleated blood cells did not exhibit NIF. In MM, most cells that exhibited bright NIF were plasmacytes. The percentage of plasmacytes with NIF ranged from 3-82%. Large fluorescent nucleoli that were difficult to classify are described. All other cells in MM bone marrows did not exhibit bright NIF. Bright NIF was noted in groups of lymphocytes and solitary lymphocytes infiltrating CLL bone marrows. These cells usually contained one or two relative large fluorescent nucleoli; the number of nucleoli corresponded with that found after staining. The results indicated that NIF produced by incubation of bone marrow smears with HeLa cell nucleoli antibodies is limited to leukemic and myeloma cells. (15 Refs)

14. THE EFFECT OF CYTOTOXIC T-LYMPHOCYTES (CTL) ON AUTOLOGOUS HUMAN PLASMACYTOMA CELLS (MEETING ABSTRACT).

Bombik BM, Hagner G
No affiliation given
Tenth International Symposium for Comparative Research on Leukemia and Related Diseases, August 31-September 4, 1981, Los Angeles, California. The Association 187 pp., 1981.

Cytotoxic T-Cells from patients with plasmacytomas were generated by culturing T-Cells from the peripheral blood of these patients together with irradiated autologous or allogeneic plasmacytoma cells as well as with a pool of normal lympho-

cytes from unrelated healthy donors. The cytotoxicity was measured by a standard chromium-release test. Target cells were the autologous and allogeneic plasmacytoma cells, and also the peripheral lymphocytes of these patients which served as a control. In addition, the CTL were cultured in T-Cell growth factor (TCGF) containing medium for several wk and the degree of cytotoxicity was determined periodically in order to see, whether long term incubation in the presence of TCGF would enhance the cytotoxic effect. In parallel experiments the plasmacytoma cells, which served as the target cells and also the plasmacytoma cells serving as stimulating cells were pretreated a short time with neuraminidase to enhance the cytotoxic effect. (no Refs)

15. UTILIZATION OF MONOCLONAL ANTIBODY IN A SOLID PHASE IMMUNOASSAY FOR CEA (MEETING ABSTRACT).

Ulrich T, Tribby I, George S, Tomita J
Abbott Laboratories, North Chicago, IL, 60064
Oncodev Biol Med; AbstractsBook,1:28 1981

A series of fusion experiments using spleen cells from mice immunized with purified carcinoembryonic antigen (CEA) and mouse myeloma cell line P3 or SP2/0 has resulted in several stable hybridomas producing monoclonal antibody with CEA binding activity. Analysis of monoclonal antibody preparations resulting from each fusion indicated that 10-50% of the hybridomas obtained were producing antibody which bound to nonspecific cross-reacting antigen as well as CEA. Several CEA specific hybridomas were propagated in mice and the ascites fluids purified by protein A Sepharose affinity chromatography. Yields of purified antibody protein ranged from 3-15 mg/ml of ascites fluid. Affinity constants of these antibodies studied were in the range of 10(9) to 10(10) liters/mole by Sip's analysis. Four CEA specific binding sites were identified by the use of monoclonal antibodies. Antibodies thus characterized were tested for their efficacy in coating polystyrene beads. Using monoclonal antibody in place of guinea pig antibody for coating beads in the present Abbott enzyme immunoassay resulted in nearly identical standard curves. Accordingly CEA values obtained on serum specimens including normals and patient sera by the monoclonal antibody system show greater than or equal to 99% correlation with present Abbott enzyme immunoassay. (no Refs)

16. MONOCLONAL ANTIBODIES TO CARCINOEMBRYONIC ANTIGEN (MEETING ABSTRACT)

Fuks A, Krantz MJ, Laferte S
McGill Cancer Center, Montreal, Canada
Oncodev Biol Med; AbstractsBook,1:P2 1981

Monoclonal antibodies to carcinoembryonic antigen (CEA) were developed by immunization of a Balb/c mouse with HCT-8R, a CEA-producing colonic adenocarcinoma cell line, and subsequent fusion of the immune splenocyte with P3-NS1/1-Ag4-1 mouse myeloma. Supernatants of hybrid cells were screened by a binding assay using purified radiolabeled CEA. Twenty-five of the 96 initial culture wells demonstrated anti-CEA reactivity and several of these have been cloned. The fine specificities of two of these antibodies were examined using radiolabeled CEA, the cross-reactive antigen 50,000 (50K), as well as proteolytic fragments derived from these molecules. The first antibody, b18.7.7, binds at high titre to CEA and to the major fragment derived from CEA by chemical cleavage at cysteine residues, as well as to the major fragment derived by trypsin, chymotrypsin or protease V8 digestion. Furthermore, this antibody reacts equally well with 50K, and its chymotryptic and protease V8 fragments. The second antibody d2.14.1, displays the same spectrum o f reactivity as b18.7.7 with CEA and its fragments but its reactivity with 50K is significantly reduced compared with that of the first antibody. We conclude that the two anti-CEA monoclonal antibodies differ in their fine specificities towards the CEA molecule. (no Refs)

17. CYTOSTATIC DRUG SENSITIVITY TESTING OF MYELOMA COLONY FORMING STEM CELLS: AN APPROACH TO INDIVIDUALIZE CHEMOTHERAPY (MEETING ABSTRACT).

Ludwig H, Fritz E, Potzi P
Department of Medicine II, University of Vienna, Vienna, Austria
Twelfth International Congress of Chemotherapy, July 19-24, 1981, Florence, Italy. The International Society of Chemotherapy 301 pp., 1981.

In 24 patients with multiple myeloma 34 prospective and 4 retrospective clinical trials were performed comparing in vitro with in vivo sensitivity to cytostatic drugs. In addition, chemosensitivity testing was repeatedly carried out in 7 patients after intensive chemotherapy and in 5 patients untreated during the test intervals. Myeloma stem cell colony growth was induced by plating 5x10(5) isolated mononuclear bone marrow cells on nutritives-supplemented autologous and allogeneic plasma clots. For chemosensitivity testing the cells were preincubated with two concentrations of 10 different cytostatic drugs. In 28 out of 34 prospective trials clinical improvement corresponded to cytostatic drug sensitivity determined in vitro amounting to a predictive accuracy of 82.3% for the test system. In the 4 patients in whom retrospective analysis only was possible, in vivo chemoresistance correlated with in vitro unresponsiveness to the drugs applied for therapy. Repeated cytostatic drug sensitivity in 5 untreated patients and 7 patients under intensive chemotherapy during test intervals indicated the emergence of more resistant tumor cell clones especially in those patients receiving therapy. In conclusion, selection of cytostatic drugs according to the results of in vitro antiproliferative drug sensitivity testing of myeloma stem cells should improve the efficiency of subsequent chemotherapy. Furthermore, the surveillance of evolving resistant tumor cell clones by periodical reevaluation of the patient's sensitivity status may add a new dimension to the treatment regimens for multiple myeloma. (no Refs)

18. MONOCLONAL ANTIBODIES AGAINST THE CELL SURFACE ANTIGEN OF HUMAN MELANOMA (MEETING ABSTRACT).

Nishiyama K, Kaneko H, Hori K, Ohashi A, Inuo T, Tsuchiya S, Hellstrom I, Hellstrom KE
Second Dept. Surgery, Yokohama City Univ., Sch. Medicine, Minamiku, Yokahama 232, Japan
Proceedings of the 9th Annual Meeting of Japan Society of Clinical Immunology held in Tokyo, 13-15 June, 1981. Japan Society of Clinical Immunology, Saitama Pref. 350-04, Japan, 239 pp., 1981.

Three-mo-old BALB/c mice were immunized with human melanoma cells. Their spleen cells (80 x 10(6)) were hybridized with mouse myeloma cells (NS-1 cells) (20 x 10(6)) by using polyethylene glycol, and a hybridoma was prepared in a hypoxanthine-aminopterin-thymidine selection medium. The supernatant of the culture medium was examined by 125I-protein assay to select a hybridoma producing antibodies against melanoma, and it was cloned. This antibody reacted specifically with 17 out of 27 types of melanoma, and with some renal and breast cancers, but not with 15 types of fibroblasts, 3 types of

B-cell lines, 2 types of normal lung cells or 4 types of fetal cells (fetal skin, fetal colon, 2 types of fetal ovary). By using the radioimmunoprecipitation assay, this antibody was found to be an IgG1 antibody against the melanoma cell surface antigen, and to have a mol wt of about 210,000. (no Refs) (In JPN)

19. MAPPING OF IMMUNOGLOBULIN VARIABLE REGION GENES: RELATIONSHIP TO THE 'DELETION' MODEL OF IMMUNOGLOBULIN GENE REARRANGEMENT.

Selsing E, Storb U
Dept. Microbiology and Immunology, SC-42, Univ. Washington, Seattle, WA, 98195
Nucleic Acids Res; 9(21):5725-5735 1981

Five families of variable region genes of mouse kappa chains were analyzed by Southern blot hybridization to determine their relative chromosomal map positions. Map positions were deduced by Vkappa gene deletion from antibody-producing cells expressing upstream Vkappa genes and retention in cells expressing downstream genes. The Vkappa regions expressed in the myelomas MOPC167, MPC11, MOPC21 and ABPC20 are members of Vkappa families exhibiting one, three, six and six major germline hybridization bands respectively. The gene order of the five families in germline DNA was found to be VM167-VM11-(VM21, VA20) - VABE8-Jkappa - Ckappa. As expected in a deletion model of Ig gene rearrangement, a sequence located just 5' of J1 in germline DNA was found to be absent from some antibody producing cells which had not retained any germline Ckappa genes. However, other cell lines contained this sequence in rearranged contexts, suggesting that any deletion model of Ig V-J joining, as well as V gene mapping, must take into account the possibilities of stepwise rearrangements and reintegration of 'deleted' DNA. (Author abstract) (17 Refs)

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CLINICAL EVALUATION AND TREATMENT OF MULTIPLE MYELOMA AND OTHER GAMMOPATHIES

SERIES CT13 No. 82/05

MAY, 1982

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DIAGNOSIS

1. ELECTRON MICROSCOPIC STUDY OF INTRANUCLEAR INCLUSION BODIES IN IGA MYELOMA CELLS.

Matsumoto K, Katayama Y, Yagihashi S, Kitaoka M
First Dept. Pathology, Hirosaki Univ. Sch. Medicine, Hirosaki, Japan
Hirosaki Igaku; 33(2):303-311 1981

Manner of formation of intranuclear inclusion bodies in IgA (gamma) myeloma cells from a 56-yr-old man was studied with the aid of electron microscopy. Optical microscopic examination of the myeloma cells showed that the inclusion bodies were round shaped, homogeneous, and unstructured and that they were present in approx 34% of the myeloma cells. The inclusion bodies were diffusely and weakly stained by PAS, and were unstained by methyl green-pyronin, and gave negative results in diastase digestion experiments. The electron microscopic examination showed that the intranuclear inclusion bodies were 1-4 m icrons large and that clumps of chromatin were present in the surrounding nucleoplasm. The inclusion bodies were enveloped by a single-layer membrane and consisted of homogenous, low to medium electron dense materials.

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An infundibular communication was observed between perinuclear cisternae and the intranuclear inclusion bodies, indicating that the inclusion bodies originated from the perinuclear cisternae. (23 Refs) (In JPN)

2. THE CLINICAL ASPECTS OF BICLONAL GAMMOPATHIES: REVIEW OF 57 CASES.

Kyle RA, Robinson RA, Katzmann JA
Mayo Clinic and Mayo Foundation, Rochester, MN, 55905
Am J Med; 71(6):999-1008 1981

Between 1966 and 1979, biclonal gammopathy was recognized in 57 patients. Clinical and laboratory features differentiated three groups: biclonal gammopathy of undetermined significance, 37 cases (65%); multiple myeloma, 9 cases (16%); and lymphoproliferative disease - including lymphoma, macroglobulinemia, chronic lymphocytic leukemia and unclassified lymphoproliferative disorders -11 cases (19%). With biclonal gammopathy of undetermined significance, symptomatic multiple myeloma developed after 2 yr in one patient; the others remained stable. One patient with multiple myeloma had osteosclerotic myeloma and a severe sensorimotor peripheral neuropathy, and another presented with plasma cell leukemia. In the remainder response to therapy and survival were much the same as in patients with multiple myeloma with a monoclonal protein. Patients with lymphoproliferative disease responded to chemotherapy like that for monoclonal gammopathy. Of the 57 patients, 30 (53%) had IgG and IgA components, 15 (26%) had IgG and IgM, 6 had two IgG components, 3 had IgA and IgM, 1 had two IgA proteins, 1 had IgA and IgE and 1 had triclonal gammopathy. Of the 115 light chains, 70% were kappa; the chains were both kappa or both lambda in 63% of biclonal pairs. In many cases, serum electrophoresis produced only a single band on the acetate strip, and the biclonal gammopathy was not recognized until immunoelectrophoresis was done. Although the clinical features of biclonal gammopathy and its response to therapy are similar to those of monoclonal gammopathy, this subject is of importance because of the lack of clinical data in the literature. (Author abstract) (96 Refs)

3. QUANTITATIVE CYTOLOGY IN MYELOMA RESEARCH (MEETING ABSTRACT).

Barlogie B, Alexanian R, Latreille J, Smallwood L, Swartzendruber D, Maddox AM
M.D. Anderson Hospital and Tumor Institute, Houston, TX, 77030
VIII Conference on Analytical Cytology and Cytometry, May 19-25, 1981, Wentworth-by-the-Sea, New Hampshire Memorial Sloan-Kettering Cancer Center; 1981

The previously reported high incidence of DNA flow cytometrically detectable incidence of aneuploidy in patients with multiple myeloma has been further validated in 161 patients, with an overall incidence of 70%, regardless of disease status. A 75% incidence of aneuploidy in patients with active disease exceeded the 15% noted in patients studied in remission. We will report on the frequency distribution patterns of ploidy levels as a function of disease status at time of study (diagnosis, remission, relapse, primary treatment failure), tumor burden, M-protein type and concentration. Overall survival of a subgroup of patients was found to be effected by ploidy level and pre-treatment tumor cell labelling index, regardless of tumor burden at diagnosis. Additional measurements of RNA content, which was found to be markedly higher in plasma cells than in any other hemopoietic cells, proved to be helpful in identifying the occasional patient with a diploid high RNA content tumor cell population. Evaluation of peripheral blood in 30 patients without plasma cell leukemia indicated 4 instances of discrete ploidy abnormality of the same degree as was found in marrow or extramedullary sites. With a median follow-up time in patients with serial observations of approx 1-2 yr, definitive evidence of ploidy changes with the development of drug resistance appears rare. Preliminary data will be presented on the feasibility and additional usefulness of CIg and nucleolar antigen content measurements. (no Refs)

4. CORRELATIONS BETWEEN DNA STEMLINE RNA CONTENT AND PARAPROTEIN LEVELS IN MULTIPLE MYELOMA (MEETING ABSTRACT).

Walle A, Andreeff M, Melamed MR, Clarkson BD
Memorial Sloan-Kettering Cancer Center, New York, NY
VIII Conference on Analytical Cytology and Cytometry, May 19-25, 1981, Wentworth-by-the-Sea, New Hampshire Memorial Sloan-Kettering Cancer Center; 1981

Twenty-nine patients with multiple myeloma (mM) were investigated at the time of presentation at Memorial Hospital. Fourteen patients were treated, fifteen untreated. DNA and RNA content was measured by acridine orange flow cytometry. Bone marrow plasma cell counts, serum and urine paraprotein levels were also determined. Data was analyzed for possible correlations between DNA stemlines, cellular RNA content of G1 cells, expressed as RNA-Index RI, cell kinetics and immunoglobulin levels in treated and untreated patients. The group of mM with diploid DNA stemline (66%) was distinctly different from the group with hyperdiploid DNA stemline (34%): paraprotein levels were lower (diploid: 278%, hyperdiploid: 570% increased above upper normal limit (IUNL), RNA content was lower (RI: 15.5; hyperdiploid: 27.7), and the number of cells in G1 with high RNA content was also lower (G1H equals 31.1%; hyperdiploid: 71.2%). No difference was found in the number of marrow plasma cells in the diploid (43%) and hyperdiploid (50%) untreated group. Cell cycle analysis did not show a difference in the number of S + G2 + M cells between untreated (10%) and treated patients (10%). RNA content was the same in treated and untreated patients: treated group: diploid RI equals 16.8; hyperdiploid RI equals 27.2; untreated group: diploid RI equals 14.1; hyperdiploid RI equals 28.0. Paraprotein levels, however, were lower in the treated groups (diploid: untreated 305% IUNL, treated 246% IUNL; hyperdiploid: untreated 790% IUNL, treated 423% IUNL. IgA myelomas had higher paraprotein (1148% IUNL) than IgG myelomas (256% IUNL). The prognostic value of the parameters investigated, alone or in combination, will be determined in a prospective study. (1 Ref)

5. WHOLE BODY BONE SCINTIGRAPHY COMPARED TO CONVENTIONAL RADIOGRAPHY IN DETECTING BONE LESIONS IN MULTIPLE MYELOMA.

Deding A, Ingeberg S, Jorgensen PS
Medical Dept. BN, Aalborg Hosp., DK-9000 Aalborg, Denmark
Dan Med Bull; 28(5):207-209 1981

In a consecutive series of 30 patients with multiple myeloma, whole body scan with 99mTechnetium methylenediphosphonate and radiographic skeletal survey were performed. The skeleton was divided into 29 bone regions; the positive regions, ie, those with increased uptake on scan and typical myelomatous lesions on x-ray, were registered and the results of the two investigations compared. Two hundred and twenty-six bone regions were positive on x-ray and/or scan, 159 (70%) on x-ray only, 26 (12%) on scan only and 41 (18%) on both x-ray and scan. None of the patients had bone lesions which were only demonstrated on scan. Almost all regions

with bone pain were positive on both x-ray and scan. The results indicate that whole body bone scintigraphy is considerably less sensitive than conventional radiography in detecting myelomatous bone lesions, and of little use as a screening procedure for determining the extent of bone involvement. (Author abstract) (15 Refs)

CLINICAL IMMUNOLOGY AND IMMUNOTHERAPY

6. CIRCADIAN VARIATIONS OF PHOSPHOHEXOSE-ISOMERASE (PGI) IN MULTIPLE MYELOMA.

Neri B, Ciapini A, Comparini T, Guidi G, Guidi S, Lupi R, Romano S
Clinica Medica Generale II, Cattedra di Semeiotica Medica Universita degli Studi di Firenze, Firenze, Italy
Eur J Cancer Clin Oncol; 17(11):1177-1181 1981

One of the problems common to all research on the neoplastic cell is that of establishing whether the differences that exist between normal and neoplastic activity are in direct relation to the transforming phenomenon or if they represent, instead, secondary or overlapping phenomena. Warburg, in 1924, first produced evidence of a higher rate of aerobic glycolysis in neoplastic tissue than in normal tissue, which is correlated with the disdifferentiation and growth rate of the tumor. Our research concerned the study of phosphohexose-isomerase (PGI) a glycolytic cycle enzyme (properties) from a chronobiological point of view in a group of 11 'healthy' subjects and in a group of 11 patients with multiple mye loma. The data obtained were analyzed using the 'group mean cosinor' method; the rhythm parameters (mesor, amplitude, acrophase) were compared using adequate statistical methods. The elaborated data show a significant circadian rhythm in both the 'healthy' subjects and in the patients affected by myeloma; in particular, we noted a significant difference between the 'mesors' and the 'amplitudes' of the two groups expressed in per cent. Moreover, these results exclude any possible effect of sex and age upon PGI activity in the serum. (Author abstract) (19 Refs)

SUPPORTIVE CARE

7. INFLUENCE OF TREATMENT AND RESPONSE STATUS ON INFECTION RISK IN MULTIPLE MYELOMA.

Perri RT, Hebbel RP, Oken MM
Dept. Medicine, Hematology Section (111E), Veterans Admin. Medical Center, 54th St. and 48th Ave. South, Minneapolis, MN, 55417
Am J Med; 71(6):935-940 1981

The clinical course of 60 patients with multiple myeloma was examined for risk factors associated with infection. The overall incidence of infection was 1.46 per patient-yr. The greatest risk period for the occurrence of infection was the first 2 months after the start of initial chemotherapy. The incidence of infection during this period was 4.68 infections per patient-yr compared with 1.04 infections per patient-yr for subsequent months. Serum creatinine levels of 2 mg/dl or more (p less than 0.03) and decreased polyclonal serum immunoglobulins (p less than 0.01) predicted increased risk of early infections. Patients infected during the first 2 mo of initial chemotherapy had the same rate of infection during the subsequent clinical course as did patients free of infection during the early treatment period. Thus, the early risk period does not represent only the attrition of susceptible patients. Patients who achieved an objective response had a decrease in infection risk during the time of the response (0.44 infections per patient-yr). While response to chemotherapy prolongs life in multiple myeloma, the initiation of chemotherapy is associated with a definable risk period for infections. (Author abstract) (25 Refs)

CASE REPORTS

8. EXTRAMEDULLARY PLASMACYTOMA OF THE SMALL INTESTINE: FIRST CASE REPORT OF ILEOCOLIC FISTULA AND REVIEW OF THE LITERATURE.

Fendel EH, Fazio VW
Cleveland Clinic Foundation, 9500 Euclid Ave., Cleveland, OH, 44106
Dis Colon Rectum; 24(8):633-635 1981

Extramedullary plasmacytoma (EMP) of the small bowel is a rare entity previously reported as a cause of intestinal obstruction or bleeding. A case report of this disease entity presenting as an ileocolic fistula is reported. EMP is diagnosed by the following criteria: (1) absence of paraproteinemia; (2) absence of Bence Jones proteinuria; (3) normal skeletal survey; and (4) normal bone marrow biopsy specimen. Gastrointestinal plasmacytoma often occurs as a manifestation of multiple myeloma. EMP of the gas trointestinal tract is a rare manifestation of the disease, accounting for 13% of all cases of EMP. It is a slow-spreading, radiosensitive tumor with a high tendency toward local recurrence. Surgical excision combined with radiotherapy is the treatment of choice for EMP of the gastrointestinal tract. (Author abstract) (18 Refs)

9. NODULAR MIXED CELL LYMPHOMA WITH MONOCLONAL GAMMOPATHY.

Bain GO, Belch A
Cross Cancer Inst., 11560 University Ave., Edmonton, Alberta T6G 1Z2, Canada
Am J Clin Pathol; 76(6):832-837 1981

Malignant lymphomas are rarely accompanied by a serum M component. Such neoplasms are usually of lymphocytic cell type and, with extremely rare exceptions, of diffuse pattern. A patient with an unusual malignant lymphoma of mixed cell type characterized by follicular structures and vascular proliferation was found to have a serum monoclonal gammopathy (IgM kappa) of over 4 g/dl. Remission accompanied by a pronounced reduction in the M protein was achieved with Chlorambucil. Subsequent relapse was characterized by the emergence of a large cell lymphoma with IgM kappa surface immunoglobulin. No concomitant rise in the serum M component accompanied relapse. (Author abstract) (18 Refs)

SELECTED PRE-CLINICAL STUDIES

10. DEVELOPMENT OF IN VITRO ASSAYS FOR MYELOMA COLONY FORMING CELLS (MEETING ABSTRACT).

Hamburger AW
American Type Culture Collection, Rockville, MD, 20852
Third NCI-EORTC Symposium on New Drugs in Cancer Therapy, October 15-17, 1981, Brussells, Belgium European Organization for Research on Treatment of Cancer; :A19 1981

This presentation summarizes the development of in vitro assays which permits formation of colonies of human monoclonal plasma cells in semi-solid media. The assay developed at the University of Arizona can be described as follows. Colony growth was induced with either 0.02ml of human RBC or 0.25ml of medium conditioned by the adherent spleen cells of mineral oil primed Balb/c mice. After 2-3 wk in culture, up to 500 colonies appeared, yielding a max plating efficiency of 0.1%. The number of myeloma colonies formed as proportional to the number of cells plated between concentrations of 10(5) to 10(6). Morphological, histochemical, and functional criteria showed that colonies consisted of immature plasmablasts and mature plasma cells. This assay was used to define a number of biophysical and immunological properties of the myeloma colony forming cells (MCFCS). Attempts have also been made to develop a monoclonal antibody against plasma cell antigens and to test its effect of MCFCs. Due to variability of the conditioned media in supporting myeloma colony growth, other investigators have devised alternative culture methods for MCFCs. The method described by Izaguirre depends on 1) exhaustively depleting cell suspensi ons of T lymphocytes, 2) a medium conditioned by T lymphocytes in the presence of phytohemagglutinin (PHA) and 3) irradiated autologous or homologous T lymphocytes. Plating efficiencies were increased up to 1-2% by this method. Ludwig and Swetly also devised a method for cloning myeloma cells in plasma clot cultures and assessed the effect of interferon on cells from 17 patients. The specific factors that support the growth of MCFCs in these systems are unknown. The assay for MCFCs correctly predicted clinically meaningful drug sensitivity with 79% accuracy and resistance with 95% accuracy for a number of myeloma patients. (no Refs)

11. EXPERIMENTAL THERAPEUTIC AND BIOCHEMICAL STUDIES OF ANTHRACENEDIONE DERIVATIVES (MEETING ABSTRACT).

Johnson RK, Broome MG, Howard WS
Arthur D. Little, Inc., Cambridge, MA, 02140
Third NCI-EORTC Symposium on New Drugs in Cancer Therapy, October 15-17, 1981, Brussels, Belgium European Organization for Research on Treatment of Cancer; :A32 1981

The anthracenedione derivatives, mitoxantrone and ametantrone, are highly active drugs in a number of experimental tumor models. These agents are curative in mice bearing ip tumors including: P388 leukemia, L1210 leukemia, B16 melanoma, colon carcinoma 26, ADJ-PC6 plasmacytoma, and M5076 ovarian carcinoma. Mitoxantrone but not ametantrone retained considerable activity against systemic (iv) leukemias. Neither agent was highly effective against sc implanted solid tumors. Sublines of P388 leukemia resistant to various DNA binders (doxorubicin, daunorubicin, amsacrine or ellipticine) were cross-resistant to mitoxantrone and ametantrone. A subline of P388 leukemia resistant to mitoxantrone was isolated and was found to be cross-resistant to ametantrone, a number of other DNA binders, and surprisingly, to alkylating agents such as melphalan, mitomycin C, and chlorambucil. The biochemical and cytotoxic effects of mitoxantrone and ametantrone were compared to those of doxorubicin in P388 cells in vitro. All three drugs had similar growth inhibitory with an IC50 of about 8 x 10(-8) M for a 48 hr continuous exposure. Using a soft agar cloning assay for cytotoxicity, it was found that mitoxantrone gave first-order cell kill kinetics essentially independent of duration of drug exposure. Ametantrone and doxorubicin had biphasic cell kill curves which were strongly dependent on duration of exposure. Mitoxantrone and ametantrone were more effective inhibitors of DNA as compared to RNA synthesis whereas, at any given concentration, doxorubicin inhibited both pathways to a similar extent. (no Refs)

12. SELECTED ASPECTS OF THE IMMUNOBIOLOGY AND IMMUNOTHERAPY OF THE MOPC-315 PLASMACYTOMA.

Przepiorka D
University of Illinois at the Medical Center, Chicago, IL
Diss Abstr Int [B]; 42(5):1815-B 1981

In vitro immunization of spleen cells from normal BALB/c mice with mitomycin C-t reated MOPC-315 cells resulted in high levels of anti-MOPC-315 cytotoxic activity as assessed by the 51Cr release assay, whereas in vitro immunization of spleen cells from mice bearing large sc MOPC-315 tumors resulted in virtually no antitumor activity. The purpose of this study was to devise a method to augment the anti-MOPC-315 response of the tumor-bearer spleen cells. The problem was approached in two ways. The first was an attempt to identify the possible suppressor cells and deplete them from the spleen cell preparation prior to in vitro immunization. The second approach was to add an immunomodulating agent to the immunization cultures. Spleen cells from mice bearing 15 to 26 mm (but no 29 mm) sc MOPC-315 tumors exhibited substantial levels of in vitro anti-MOPC-315 activity after they were cultured for 5 days in medium containing 2% polyethylene glycol 6000 (PEG) with or without added stimulator cells. Finally, tumor-bearer spleen cells from culture with PEG were far superior to spleen cells cultured without PEG in mediating anti-MOPC-315 activity in vivo in a local adoptive transfer assay and in systemic chemoimmunotherapy of an established sc tumor. Thus, autologous lymphoid cells cultured in PEG might be useful in immunotherapeutic regimens requiring histocompatible cells with augmented antitumor activity but devoid of activity against normal cells. (no Refs)

13. INHIBITION OF CUTANEOUS ANAPHYLAXIS AND ARTHUS REACTIONS IN THE MOUSE BY ANTIGEN-SPECIFIC IGA.

Russell-Jones GJ, Ey PL, Reynolds BL
(c/o Ey) Dept. Microbiology and Immunology, Univ. Adelaide, GPO Box 498, Adelaide 5001, Australia
Int Arch Allergy Appl Immunol; 66(3):316-325 1981

The nitrophenyl-specific IgA myeloma protein secreted by the MOPC-315 mouse plasmacytoma was examined for its capacity to inhibit antibody-mediated hypersensitivity reactions in the mouse. Specific inhibition of both cutaneous anaphylactic and complement-dependent (Arthus) reactions was observed in sensitized mice when the eliciting antigen was mixed with IgA prior to injection or when the mice were injected with plasmacytoma cells and possessed detectable amounts of MOPC-315 IgA in their serum at the time of challenge. The possibility that IgA antibodies have a role in suppressing hy-

persensitivity reactions at mucosal surfaces is discussed. (Author abstract) (31 Refs)

14. GENERATION OF MONOCLONAL ANTIBODIES REACTING WITH HUMAN NORMAL AND NEOPLASTIC MAMMARY DUCT EPITHELIAL CELLS (MEETING ABSTRACT).

Menard S, Colnaghi MI, Tagliabue E, Canevari S, Fossati G, Sonnino S

Istituto Nazionale Tumori, Milano, Italy

Hybridomas and Cellular Immortality (Second Houston Symposium), November 5-6, 1981, Houston, Texas. University of Texas Medical School at Houston 55 pp., 1981.

A monoclonal antibody was obtained from a hybridoma line generated by the fusion of P3 myeloma cells with spleen cells of a mouse immunized with cell membrane extracts from the human breast cancer cell line MCF-7. The specificity was studied by isotopic immunoglobulin assay on several cell lines and cell membrane extracts from various surgical specimens and milk cells; by membrane immunofluorescence on cell lines and cell suspensions obtained from fresh tumors; by immunofluorescence and immunoperoxidase technique on histological slices from about 100 different normal or neoplastic tissues. The structure recognized by the monoclonal antibody was found on normal epithelial cells of mammary duct and on 80% of the 50 breast carcinomas tested. The antigenic activity was unaffected by treatment with trypsin, Vibrio cholerae neuraminidase and by heating the cells at 100C but was inactivated by treatment with methanol. When lipid extracts for MCF-7 membrane preparations were chromatographed on diethylaminoethyl cellulose Sephadex the antigenic activity was recovered only on the neutral ganglioside fraction. (no Refs)

15. MONOCLONAL ANTIBODIES TO HUMAN PROSTATE AND BLADDER TUMOR ASSOCIATED ANTIGENS (MEETING ABSTRACT).

Starling JJ, Wright GL

Eastern Virginia Medical School, Norfolk, VA, 23501

Hybridomas and Cellular Immortality (Second Houston Symposium), November 5-6, 1981, Houston, Texas. University of Texas Medical School at Houston 55 pp., 1981.

Monoclonal antibodies to human prostate adenocarcinoma membrane antigens were produced by fusion of spleen cells from Balb/C mice immunized against the prostate cancer cells line DU145, and the P3X63/Ag8 mouse myeloma line. The hybrids were screened for antibody production using glutaraldehyde-fixed or live cells in an in vitro binding radioimmunoassay (RIA). Antibody binding specificity was also checked by quantitative adsorption studies. A hybridoma clone (83.21) was isolated that secreted antibodies which preferentially bound to prostate and bladder cancer cells but did not bind to a variety of other normal and malignant human cell lines. This antibody also reacted with a cytomegalovirus-transformed human embryonic lung cell line but not to normal human embryonic lung cells. Conventional and competitive binding studies indicate that the 83.21 monoclonal antibody does not bind to alpha-fetoprotein, carcinoembryonic antigen, prostatic acid phosphatase, human WBC antigen (HLA), beta2 microglobulin, fibronectin, prostate specific antigen or DR antigens. Preliminary immunoprecipitation data with 125I-labeled, detergent soluble, DU145 membrane proteins and the 83.21 monoclonal antibody suggest that this antibody binds two proteins with mol wt of 210 and 97 kilodaltons. (no Refs)

16. CELL SURFACE ANTIGENS OF X-RAY INDUCED LYMPHOMA: DETECTION AND CHARACTERIZATION USING MONOCLONAL ANTIBODIES (MEETING ABSTRACT).

Allison JP

The University of Texas System Cancer Center, Science Park, Smithville, TX, 78957

Hybridomas and Cellular Immortality (Second Houston Symposium), November 5-6, 1981, Houston, Texas. University of Texas Medical School at Houston 55 pp., 1981.

The cell surface antigenic mosaic of an x-ray induced lymphoma of C57BL/6 mice has been examined using conventional and monoclonal antibodies. The tumor cells display four glycoproteins related to murine leukemia virus (MuLV) - two env and two gag gene products. Immunization of syngeneic mice with tumor cells elicited formation of antibodies to only one of the two MuLV env proteins. Analysis with monoclonal antibodies revealed that this antigen was antigenically related to ecotropic MuLV. One hybridoma clone, designated 124-40, produced by fusion of spleen cells from C6XL-immunized BALB/c mice with P3 myeloma cells, secreted monoclonal antibodies (McAb) which reacted with tumor cells, but not with normal lymphoid cells. The tumor associated antigen reative with McAb 124-40 was found to be a glycoprotein with subunit mol wt of approx 40 Kd, and was structurally and immunologically distinct from MuLV antigens on the tumor cells. The antigen was not found on adult spleen, thymus, bone marrow, or lymph node cells, nor on fetal thymus or spleen. Two additional x-ray lymphoma lines, as well as three spontaneous leukemias of AKR mice, were also unreactive with McAb 124-40. Administration of the McAB 124-40 to tumor-bearing mice resulted in a slight increase in survival time. The therapeutic effect was greatly enhanced by administration of McAb conjugated to the cellular toxin pokeweed antiviral protein. (no Refs)

17. A NEW NON-IMMUNOGLOBULIN PRODUCING HUMAN MYELOMA CELL LINE FOR PRODUCTION OF HYBRIDOMAS (MEETING ABSTRACT).

Pickering JW, Gelder FB

Department of Microbiology/Immunology and Surgery, Louisiana State University Medical Center, Shreveport, LA, 71130

Hybridomas and Cellular Immortality (Second Houston Symposium), November 5-6, 1981, Houston, Texas. University of Texas Medical School at Houston 55 pp., 1981.

We selected an 8-azaguanine resistant mutant of a human myeloma cell line (RPMI 8226) by cloning the parental cells on a feeder layer of mouse spleen cells in the presence of increasing concentrations of 8-azaguanine. Culture media and cell-free extracts of both the parental and mutant (8226 AR/NIP4-1) cell lines were assayed for immunoglobulin heavy and light chain by Ouchterlony double immunodiffusion and for lamda chain by radioimmunoassay. Secretion of free lamda chain by the parental cell line was confirmed. In contrast, no immunoglobulin heavy or light chains were detected in culture medium of the mutant cell line by either immunodiffusion or radioimmunoassay. No intracellular lamda chain could be detected in the mutant cells by radioimmunoassay of cell free extracts or by immunofluorescence of fixed cells. Hybridomas were produced by fusion of 8226AR/NIP4-1 cells with lymphocytes from a mesenteric lymph node recovered at surgery from a hypertransfused renal transplant recipient. Twenty hybrid culture media were assayed for immunoglobulin by double immunodiffusion and 15 contained either IgG (lamda) or IgG (kappa). None produced IgM or IgA. One hybridoma producing IgG (kappa) was shown by immunofluorescence not

to reexpress lamda chain of the parental myeloma. Hybrid antibodies were screened for reactivity in a lymphocyte microcytotoxicity assay against a panel of 46 normal human donors. One hybrid antibody lysed 50% of peripheral lymphocytes from 4 of the donors. This antibody appeared to recognize an alloantigen present on a subpopulation of human lymphocytes. (no Refs)

18. MONOCLONAL ANTIBODIES SPECIFYING TUMOR ASSOCIATED ANTIGENS AND THEIR POTENTIAL FOR DIAGNOSIS AND THERAPY (MEETING ABSTRACT).

Baldwin RW
Cancer Research Campaign Laboratories, University of Nottingham, Nottingham, NG7 2RD, England
Hybridomas and Cellular Immortality (Second Houston Symposium), November 5-6, 1981, Houston, Texas. University of Texas Medical School at Houston 55 pp., 1981.

Monoclonal antibodies specifying cell surface antigens on normal and malignant cells provide probes for investigating cell membrane changes in malignant transformation and for developing new approaches to cancer detection and treatment. Monoclonal antibodies directed against antigens associated with a naturally arising rat mammary carcinoma (Sp4) are produced by an interspecies hybridoma derived from a fusion of spleen cells from a syngeneic Sp4-immune rat with P3NS1 mouse myeloma cells. These antibody preparations (Sp4/A4) react specifically with tumor Sp4 cells when tested by membrane immunofluorescence or radioimmunoassays. The expression of Sp4 antigen on cells derived from tumors has also been demonstrated by analysis in the Fluorescence Activated Cell Sorter so providing a quantitative procedure for the analysis of cells derived from in vivo tumors. Sp4/A4 monoclonal antibody (rat IgG gamma 2b, mouse K chain) labelled with 125I specifically localizes in Sp4 tumor growing sc in syngeneic rats. Tumor localization was also demonstrated using 125I-labelled antibody by whole body gamma scintigraphy after 99mTc labelled blood pool subtraction. The therapeutic potential of conjugates of this antibody preparation conjugated to adriamycin have been evaluated. Adriamycin conjugated to antibody via a dextran bridge retained cytotoxic activity as assayed by an in vitro target cell survival. The conjugates also retained antibody activity binding to tumor Sp4 but not unrelated tumors. When tested in vivo the conjugates showed enhanced therapeutic effectiveness when tested against sc tumor grafts. (no Refs)

19. HUMAN HYBRIDOMAS (MEETING ABSTRACT).

Croce CM
The Wistar Institute of Anatomy and Biology, 36th Street at Spruce, Philadelphia, PA, 19104
Hybridomas and Cellular Immortality (Second Houston Symposium), November 5-6, 1981, Houston, Texas. University of Texas Medical School at Houston 55 pp., 1981.

Human myeloma cells were mutagenized and selected for deficiency in hypoxanthine phosphoribosyltransferase (HPRT). HPRT deficient mutants were then fused with human lymphocytes derived from patients responding to viral antigens and self antigens. Hybridomas secreting anti-viral antibodies and auto-antibodies were obtained. The use of the human hybridoma technology to study human autoimmune diseases will be discussed. (no Refs)

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CLINICAL EVALUATION AND TREATMENT OF MULTIPLE MYELOMA AND OTHER GAMMOPATHIES

SERIES CT13 No. 82/06

JUNE, 1982

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DIAGNOSIS

1. PLOIDY AND PROLIFERATIVE CHARACTERISTICS IN MONOCLONAL GAMMOPATHIES.

Latreille J, Barlogie B, Johnston D, Drewinko B, Alexanian R (c/o Barlogie) Dept. Developmental Therapeutics, Univ. Texas System Cancer Center, M.D. Anderson Hosp. and Tumor Inst., Houston, TX, 77030

Blood; 59(1):43-51 1982

Measurements were performed in 143 patients with monoclonal gammopathy of the cellular substrate in the bone marrow, including analysis of DNA and RNA content and tritiated thymidine labeling index. Aneuploidy by DNA content was present in 80% of 115 patients with active multiple myeloma and in 4 of 9 patients with benign monoclonal gammopathy, but was absent in all 12 patients with myeloma in remissi on and in 7 individuals with Waldenstrom's macroglobulinemia. With regard to prognosis in multiple myeloma, a low pretreatment plasma cell labeling index of less than or equal to 1% heralded longer survival than that observed in patients with a labeling index greater than 1%, independent of myeloma tumor burden and ploidy pattern, except for a subset of 17 patients with a low-degree hyperdiploid abnormality whose

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survival was not affected by the magnitude of the pretreatment labeling index. Thus, besides tumor burden, tumor proliferative activity and ploidy both appear to have additional prognostic importance for patients with multiple myeloma. (Author abstract) (21 Refs)

2. CHROMOSOME ANALYSIS IN MULTIPLE MYELOMA (MEETING ABSTRACT).

Balogh E, Kaszas I, Benko S, Krizsa F, Fleischmann T

2nd Department of Medicine, University Medical School, Szeged, Hungary

Ninth Congress of the Haematological Society, October 1-3, 1981, Debrecen, Hungary. The Society 175 pp., 1981.

The results of chromosome analysis of 15 patients with myeloma multiplex will be demonstrated. The clinical and immunulogical data of them will be reviewed, too. The aspiration bone marrow biopsy specimens were prepared with the method of Kiossoglou modified by the authors, and the bending of the chromosome-preparation was done with ASG or trypsin-Giemsa methods. All of the cases were diploid-grade, the aneuploidia was rare. Half of the patients had pathological cytogenetical parameters, the majority of chromosome aberrations were of clonal type. One of those cases had 17P+, while another had 14q+ anomaly. The results will be discussed in comparison with other data. (no Refs)

3. COMPARISON OF TUMOUR CELL MASS IN MULTIPLE MYELOMA MEASURED BY SYNTHETIC RATE STUDIES WITH THAT CALCULATED FROM CLINIAL STAGING SYSTEMS (MEETING ABSTRACT).

Cooper DA, Miller AC, Penny R

Department of Immunology, St. Vincent's Hospital, Sydney, Australia

Clinical Oncology Society of Australia, November 24-27, 1981, Melbourne, Australia. The Society 70 pp., 1981.

Tumor cell mass (TCM) in patients with multiple myeloma has been measured by synthetic rate studies of bone-marrow tumor cells in culture. From these measurements of Salmon and coworkers have been developed a simple clinical staging system in which TCM is calculated by a programmable pocket calculator. We have compared the measurement and calculation of TCM in patients with IgG and IgA multiple myeloma by these methods in our own laboratory. There was correlation between synthetic rate and serum IgG paraprotein concentration but not the serum IgA paraprotein concentration. In patients with IgG myeloma there was correlation between measured and calculated TCM as well as measured TCM and serum IgG paraprotein concentration, urine Bence Jones protein excretion, and serum albumin concentrat ion. Measured TCM also inversely correlated with hemoglobin concentration. In patients with IgA myeloma however, there was no correlation between measured TCM and calculated TCM or any other individual clinical laboratory parameter. A number of problems have contributed to the overall failure of this method to measure and calculate TCM including methodological differences, definition of myeloma cells, proteolysis of newly synthesized paraprotein in culture, changes in synthetic rates with time and assessment of the degree of bone lesions by skeletal roentgenograms. We cannot recommend these methods as they stand to measure and calculate TCM in patients with multiple myeloma. (no Refs)

4. IDIOTYPIC LYMPHOID CELLS IN HUMAN MYELOMA (MEETING ABSTRACT).

Seligmann M, Preud'homme JL

Hopital Saint Louis, Paris, France

Sixth Meeting of the International Society of Haematology, European and African Division, August 30 September 4, 1981, Athens, Greece. Hellenic Society of Haematology 409 pp., 1981.

Multiple myeloma is a B cell malignancy classically thought to involve primarily bone marrow plasma cells. However, in the recent yr, several laboratories including ours have reported an increased incidence of blood lymphocytes bearing and producing molecules which react with antisera to idiotypic determinants of the individual myeloma globulin of the patient. In most of the cases, these idiotypic circulating lymphocytes belong to the B series and produce a membrane-bound monoclonal immunoglobulin that shares the idiotypic determinants of the serum myeloma globulin. In one of these studies, pre-B cells, the immediate precursors of B lymphocytes, were shown to be affected. These findings suggest that the disease involves not only plasma cells but also B lymphocytes and their precursors, and they provide evidence for a very early transformation event in the myeloma cell clone. In a few cases, a fair proportion of circulating T lymphocytes were also shown to express the individually specific idiotypic determinants. These T lymphocytes synthesized membrane receptors which shared idiotypic (but not isotypic) structures of the immunoglobulin molecule produced by the malignant plasma cells and which were able to bind the same antigen. The precise meaning of this finding remains unknown. The hypothesis of a malignant T cell proliferation appears less likely than that of an expansion of immunoregulatory T cells. (no Refs)

CLINICAL IMMUNOLOGY AND IMMUNOTHERAPY

5. ALTERNATIVE PATHWAY OF COMPLEMENT IN MULTIPLE MYELOMA.

Kraut EH, Sagone AL

Ohio State Univ. Hosp., N1025, 410 West 10th Ave., Columbus, OH, 43210

Am J Hematol; 11(4):335-345 1981

The alternative pathway of complement was studied in 16 newly diagnosed and 2 previously treated patients with multiple myeloma. Functional activity of this pathway was abnormal in 10 of these 18 patients (55%). These abnormalities correlated with depressed levels of alternative pathway components in 3 of 10 patients, but in the remaining 7, no etiology was demonstrated. There was an inverse correlation between activity and concentration of the monoclonal protein. This defect is an additional factor that may predispose patients with myeloma to overwhelming infection. (Author abstract) (27 Refs)

6. OPSONIC ACTIVITY OF MYELOMA IMMUNOGLOBULINS (MM-IG).

Cheson BD

Div. Hematology-Oncology, Univ. Utah Medical Center, Salt Lake City, UT, 84132

Am J Hematol; 11(4):347-353 1981

Patients with MM are at an increased risk for life-threatening bacterial infections, primarily by organisms that require opsoni-

zation for interaction with granulocytes. In the present study we used a neutrophil chemiluminescence (CL) assay of opsonization to explore the opsonic activity of MM-Ig for zymosan particles. Particles were treated with serum lacking in Ig to explore the contribution of Ig to zymosan opsonization. This serum was found to have 69 +-2.6% (chi square +- SEM) of the opsonic activity of normal serum (p less than .001). Normal serum concentrations of normal IgG, MM-IgG, and MM-IgA all lacked opsonic activity for zymosan. However, when particles were treated with Nl-IgG, MM-IgG, or MM-IgA as well as complement, normal opsonic activity was generated. Increasing the concentration of the Ig to stimulate MM serum did not inhibit this opsonic activity. Thus both MM-IgG and MM-IgA can function as normal, nonspecific opsonins. (Author abstract) (35 Refs)

7. IMMUNOSUPPRESSION IN PLASMACYTOMA: INDUCTION OF SUPPRESSOR CELLS.

Chen Y, Hwang LT, Heller P
Hematology Section (151C), Veterans Admin. West Side Medical Center, PO Box 8195, Chicago, IL, 60680
Clin Exp Immunol; 47(1):191-196 1982

Immunosuppression in BALB/c mice with plasmacytomas (PC) is, at least in part, due to increased suppressor activity of splenic adherent cells. A PC subcellular fraction rich in intracisternal A particles, previously shown to have an immunosuppressive effect in normal BALB/c mice, is now shown to exert this effect through the development of splenic suppressor cells. The splenic suppressor cells induced with this subcellular fraction were found to be radioresistant adherent macrophages that suppressed the immune response of normal splenic cells to sheep erythrocytes through a diffusible factor, but did not influence their polyclonal IgM secretion after LPS stimulation in vitro. These characteristics are identical to those of the naturally occurring suppressor macrophages in mice with PC. Whether the induction of suppressor cells is due to the intracisternal A particles themselves or a factor co-purified with them, remains to be established. (Author abstract) (24 Refs)

CHEMOTHERAPY

8. THE TREATMENT OF PLASMA CELL MYELOMA (MEETING ABSTRACT).

Malpas JS
Department of Medical Oncology, St. Bartholomew's Hospital, London EC1A 7BE, England
Sixth Meeting of the International Society of Haematology, European and African Division, August 30 September 4, 1981, Athens, Greece. Hellenic Society of Haematology 409 pp., 1981.

Oral Melphalan or Cyclophosphamide induce partial remission in 40 to 60 per cent of previously untreated patients with plasma cell myeloma. It has been shown that cross resistance may not occur. Melphalan and Prednisolone given intermittently is used most frequently and is the combination with which other regimens are compared. In an attempt to increase the remission rate and prolong survival, Vincristine, Carmustine (BCNU), Adriamycin and Procarbazine have been added singly or in combination. Cyclophosphamide, BCNU and Prednisolone have been shown to be more effective than Melphalan and Prednisolone as a combination in a sequential study. The addition of Vincristine to Melphalan, Cyclophosphamide, Prednisolone or Cyclophosphamide, Adriamycin, Prednisolone is claimed to increase response rate and survival but this could be due to an increase in the intensity of drug administration. When Melphalan, Cyclophosphamide, BCNU and Prednisolone have been compared randomly with Melphalan and Prednisolone survival benefit has been seen in the bad prognostic category of patients but good risk groups have done less well because of toxicity. The claims for multi-drug regimens improving response and survival therefore need critical examination. (no Refs)

9. PROMISING SURVIVAL IN MYELOMA WITH FIVE-DRUG REGIMEN MOCCA (MEETING ABSTRACT).

Palva I, Ahrenberg P, Ala-Harja K, Almqvist A, Apajalahti J, Hallman H, HanninenA, Ilvonen M, Jarvenpaa E, Jarventie G, Koivunen E, Koistinen S, Katka K, Lahtinen R, Laitinen A, Lehtinen M, Palva T, Pelliniemi TT, Pulli T, Rajamaki A, Rosengard S, Tillikainen J, Timonen T, Waris E, Wasastjerna C, Vilpo J
Hatanpaa Hospital, SF-33100 Tampere 10, Finland
Sixth Meeting of the International Society of Haematology, European and African Division, August 30-September 4, 1981, Athens, Greece. Hellenic Society of Haematology 409 pp., 1981.

The Finnish Leukaemia Group has applied a modification of the five-drug regimen M-2 in a multicenter trial of treating myeloma since Jan 1, 1979. All patients fulfilling the diagnostic criteria of myeloma by SWOG and under 70 yr entered to the study in the participating hospitals until Feb 28, 1980. The response was evaluated according to the Myeloma Task Force. Treatment was vincristine 0.03 mg/kg, cyclophosphamide 10 mg/kg iv, lomustine 40 ng po on day 1, melphalan 0.25 mg/kg days 1-4 and methylprednisolon 0.8 mg/kg days 1-7, 0.4 mg/kg 8-14 (MOCCA), repeating every 5th wk. The dosage was attenuated d uring cytopenia and renal failure. One patient was excluded because of desperate condition. A 50% response was achieved in 37 out of 50 previously untreated patients (74%), and 75% reduction of myeloma protein in 14 of them (28%). Their survival is 94% at 6 mo, 79% (of 45) at 12 mo and 70% (of 33) at 18 mo. In patients resistant to or relapsing during their other treatment a response was achieved with MOCCA in 18 out of 29 (62%) and a 75% response in 3 of them. The survival in this group was 86% at 6 mo, 62% at 12 mo and 45% at 18 mo. The rate of complications was similar to other treatment for myeloma. (no Refs)

10. THERAPEUTIC RESULTS IN MULTIPLE MYELOMA (MEETING ABSTRACT).

Gociu M, Butoianu E, Munteanu N, Stoica I, Colita D, Ciocoiu A, Funduc I, Ursea C, Berceanu S
Clinic of Haematology, Fundeni Hospital, Bucharest, Romania
Sixth Meeting of the International Society of Haematology, European and African Division, August 30-September 4, 1981, Athens, Greece. Hellenic Society of Haematology 409 pp., 1981.

During the last 15 yr, 93 patients with multiple myeloma were followed up. Their classification was made after the monoclonal immunoglobulin (blood or/and urine) and staging according to the criteria of Durie and Salmon. The patients were treated with: a) single-drug chemotherapy (melphalan -30 patients, peptichemio -14 patients); b) melphalan and prednisone-3 patients, and c) combination chemotherapy (vincristine-melphalan-cyclophosphamide-prednisone) 12 patients. In patients. In patients treated with single-drug chemotherapy the mean survival was 19.9 mo, one patient is still alive. Of 37 patients treated with melphalan and prednisone 29 died with a mean survival time of 21.68 mo and 8 are still in life with a survival of +37 mo. Of patients treated with combination chemotherapy, 5 died with a mean survival of 24.8 mo, but 7 are still in life with a survival of +21.42 mo. Of 93 patients followed-up, 12 underwent complete remission with a mean duration of

25.75 mo. Our observations emphasize that in multiple myeloma treatment prednisone improves the symptomatology without influencing the survival, while combination chemotherapy seems to prolong the survival time. (no Refs)

SUPPORTIVE CARE

11. BIPHASIC PATTERN OF BACTERIAL INFECTION IN MULTIPLE MYELOMA.

Savage DG, Lindenbaum J, Garrett TJ
(c/o Lindenbaum) Dept. Medicine, Harlem Hosp. Center, New York, NY, 10037
Ann Intern Med; 96(1):47-50 1982

Since the 1960s, gram-negative bacilli have become commoner pathogens than Streptococcus pneumoniae in multiple myeloma. To investigate this trend, we analyzed 75 bacterial infections in 57 patients with myeloma. Episodes of infection with Streptococcus pneumoniae and Hemophilus influenzae occurred at presentation, early in the disease, and in patients responding to chemotherapy. Gram-negative bacill i and Staphylococcus aureus caused 80% of infections seen after diagnosis and 92% of deaths from infection. Episodes of infection with gram-negative bacteria occurred in patients with active and advancing disease and in those responding to chemotherapy when neutropenic. Impaired antibody production may be the major immune defect leading to S pneumoniae and H influenzae infections whereas some additional factor or factors related to disease activity appear to predispose to gram-negative infection in myeloma. (Author abstract) (30 Refs)

CASE REPORTS

12. IGD KAPPA PLASMA CELL DYSCRASIAS. EXTRAOSSEOUS MANIFESTATIONS INCLUDING ISOLATED LEPTOMENINGITIS.

Johnston JB, Weinerman B, Cooney T, Bowman DM, Pettigrew NM, Orr K
(c/o Weinerman), Manitoba Cancer Treatment and Res. Foundation, 700 Bannatyne Ave., Winnipeg, Manitoba, R3N 0V9, Canada
Am J Clin Pathol; 77(1):60-65 1982

IgD kappa plasma cell dyscrasias are rare. Two cases with unusual presentations and courses are described. One of these patients had myelomatous pleural effusions, and subsequently experienced myelomatous leptomeningitis. The significance of this combination is discussed and the literature reviewed. The value of immunofluorescent techniques in identifying plasma cells in the cerebrospinal fluid and pleural fluid is emphasized. (Author abstract) (43 Refs)

13. MULTIPLE MYELOMA WITH MASSIVE PLASMA - CELL ASCITES (MEETING ABSTRACT).

Gomes d' Oliveira JJ, Odette M, De Almeida OM, Carneiro de Moura M, Guerra L, Ducla-Soares A
Hospital de Santa Maria, Medicina III, Lisbon, Portugal
Sixth Meeting of the International Society of Haematology, European and African Division, August 30-September 4, 1981, Athens, Greece. Hellenic Society of Haematology 409 pp., 1981.

Ascites containing atypical plasma-cells is a rare occurrence, with no more than ten reported cases. In some it was an event associated with advanced generalized multiple myeloma, in other ascites it was in relation to IgA gastrointestinal plasmocytomas, without bone involvement. A sixty-nine-yr old white female was referred to our Department in February, 1981. She developed increasing abdominal girth and ankle swelling for the last three mo. Physical examination revealed tense ascites. Laboratory values were: Hb 12.8 gm%, human calcitonin (Hct) 40.0%, WBC 8,200/mm3, with 72% neutrophils, 23% lymphocytes and 5% monocytes, platelets 280,000/mm3, creatinine 1.0 mg%, calcium 9.2 mg%. Total serum protein was 84.5 gm/l, 35.7 gm of which was a monoclonal spike in the gamma region of protein electrophoresis. Serum immunoelectrophoresis revealed an IgG with Kappa Light-chain type. Serum IgG level was 3,948 mg%, IgA 27mg% and IgM undosable. Urinalysis showed no albumin or Bence-Jones protein. Bone marrow examination showed 18% immature plasmacytes. Bo ne films revealed scantlytic lesions in the right humerus and femur. Paracentesis yielded serosanguineous fluid containing numerous atypical plasma-cells. Total ascites protein was 61.0 gm/l, and the electrophoresis showed a 20.3 gm monoclonal spike similar to the one in serum. A plasmaphoresis was performed and melphalan and prednisone was given for 4 consecutive days. The patients expired two wk later. At autopsy there was extensive myelomatous involvement with associated generalized amyloidosis, without abdominal plasmocytomas. (no Refs)

14. TRANSFORMATION OF WALDENSTROM'S MACROGLOBULINEMIA IN A HIGH GRADE MALIGNANT LYMPHOMA OF IMMUNOBLASTIC TYPE (MEETING ABSTRACT).

Wust I, Emmerich B, Pemsl M, Lechner S, Rastetter J
Department of Haematology and Oncology, Technical University Munich, Munich, W. Germany
Sixth Meeting of the International Society of Haematology, European and African Division, August 30-September 4, 1981, Athens, Greece. Hellenic Society of Haematology 409 pp., 1981.

Transformation of a chronic hemopoetic proliferative disorder in a morphologic different acute high grade malignancy is a common event in chronic granulocytic leukemia and occurs in low incidence in some Non-Hodgkin lymphomas, but is unusual for Waldenstrom's macroglobulinemia. Clinical data will be reported from a 67 yr old male patient in whom diagnosis of macroglobulinemia was made by monoclonal IgM, enlargement of spleen, liver and abdominal lymph nodes and bone marrow aspiration and biopsy. He was treated with steroids and cyclophosphamide for three mo. Then an acute acceleration of lymph node and organ infiltration with severe hemolytic anemia developed. The monoclonal IgM was further present, and now also kappa l-chains were excreted in the urine. Bone marrow biopsy and post mortem examination revealed a disseminated high grade malignant lymphoma from immunoblastic type. The permanent production of the same M gradient suggests that both malignancies derived from one B-cell clone. (no Refs)

15. INTRACRANIAL SOLITARY EXTRASKELETAL PLASMACYTOMA RESEMBLING MENINGIOMA.

Atweh GF, Jabbour N
Div. Hematology-Oncology, Duke Univ. Medical Center, PO Box 31174, Durham, NC, 27710
Arch Neurol; 39(1):57-59 1982

Computed tomographic (CT) scan findings of a solitary extraskeletal plasmacytoma (SEP) arising intracranially are presented. The patient was a 30-yr-old woman who presented

with a 6-mo history of episodes of burning epigastric pain radiating to the chest and head and of paresthesias in both upper extremities. CT scan showed a dense homogeneous mass lesion with well-defined borders, shift of the midline structures, and extensive brain edema. Sharp enhancement was observed after contrast injection. No calcifications or bone destruction were seen. The tumor was composed of homogeneous sheets of plasma cells which we re characterized by eccentrically located nuclei with heterochromatin condensation distributed around the periphery of the nucleus as several heavy clumps. The cytoplasm was rich in rough endoplasmic reticulum and had a highly developed Golgi apparatus. A review of 12 other reported cases of SEP reveals that the clinical features, sites of involvement, and gross appearance of intracranial SEPs are similar to those of meningiomas. However, SEPs appear to be more aggressive than typical meningiomas. (18 Refs)

16. OSTEOSCLEROTIC MYELOMA. REPORT ON THREE CASES AND REVIEW OF THE LITERATURE.

Menu Y, Dhermy D, Brousse N, Grenier P, Pallardy G, Nahum H
Service de Radiologie, Hopital Beaujon, 100, av. du General-Leclerc, 92118 CLICHY Cedex, France
Sem Hop Paris; 57(45/46):1920-1924 1981

Three cases of osteosclerotic myeloma are reported. Clues for diagnosis are agarose gel electrophoresis and sclerotic bone biopsy. Review of 50 cases of literature points out frequency of peripheral neuropathy and Ig A type immunoglobulin. Iliac crest biopsy shows thickening of bone structures and plasmocytosis in medullary spaces. Main x-ray signs are mentioned and pathogenesis is discussed. (Author abstract) (26 Refs) (In FRE)

SELECTED REPORTS ON ETIOLOGY AND EPIDEMIOLOGY

17. CHRONIC LYMPHOCYTIC LEUKAEMIA AND MYELOMA: ASSOCIATION WITH ASBESTOS EXPOSURE (MEETING ABSTRACT).

Jacobson RJ, Kagan E
Departments of Medicine and Pathology, Georgetown University School of Medicine, Washington, DC, 20007
Sixth Meeting of the International Society of Haematology, European and African Division, August 30-September 4, 1981, Athens, Greece. Hellenic Society of Haematology 409 pp., 1981.

There have been comparatively few published reports of an association between asbestos exposure and hematopoietic neoplasia. However, where this relationship has been documented, a striking predominance of lymphoproliferative malignancies has been noted. We now report a series of 9 asbestos-associated lymphoid neoplasms (5 cases of chronic lymphocytic leukemia, 2 cases of IgA myeloma and 2 cases of IgG myeloma). In all instances, there was clear-cut history of prolonged occupational exposure to asbestos dust. Coexistent parenchymal asbestosis was evident in 7 subjects. In 1 individual, the asbestosis was associated with a bronchogenic carcinoma. Curiously, IgG myeloma coexisted with a malignant mesothelioma in 2 further subjects. A variety of immunologic aberrations have been observed in asbestos-exposed subjects including hyperactive B cell function. Alveolar macrophages from asbestos-dusted rats are also capable of triggering lymphoproliferation. It is conceivable, therefore, that persistent immunologic stimulation, as a consequence of of asbestos inhalation, may eventuate in lymphoid cancer such as myeloma and chronic lymphocytic leukemia. (1 Ref)

18. EPIDEMIOLOGIC DATA ON MULTIPLE MYELOMA IN AUSTRIA (MEETING ABSTRACT).

Ludwig H
Department of Medicine II, University of Vienna, Vienna, Austria
Sixth Meeting of the International Society of Haematology, European and African Division, August 30-September 4, 1981, Athens, Greece. Hellenic Society of Haematology 409 pp., 1981.

Multiple myeloma accounted for 166 (17%) of the 1064 deaths due to lymphoreticular malignancies that were registered in Austria during 1979. The age distribution at diagnosis showed an outstanding peak in the 6th decade followed by patients with manifestation of the disease in their 5th and 7th decade, with a median age at diagnosis of 67.2 yr. The age-specific incidence curve showed a sharp increase from less than 0.2 myeloma patients per 100,000 inhabitants at age 40 through 9.1 patients per 100,000 Austrians of age 70. The age-adjusted myeloma incidence rates increased steadily during the period of time between 1969 (2.7/100,000) and 1979 (3.8/100,000). The distribution of paraprotein types analyzed in a group of 114 patients revealed: IgG 59%, IgA 16%, light chain 20%, IgD 2%, biclonal 1%, and non-secretory 3%. The kappa:lambda ratio was 2.4:1, the sex incidence showed an equal distribution (male:female equals 0.96:1). In conclusion, the age-specific and age-adjusted incidence rate for multiple myeloma as well as the distribution of paraprotein types in Austria is comparable with the data reported for other European countries and for the white population of North American. The median age at diagnosis is slightly higher than in most other reported studies and no predominance of male patients was observed. (no Refs)

SELECTED PRE-CLINICAL STUDIES

19. EFFECT OF IRON DEFICIENCY ON TRANSPLANTABLE MURINE PLASMACYTOMA.

Benbassat J, Hershko C, Laskov R, Eliakim M
Dept. Medicine A, Hadassah Univ. Hosp., P.O. Box 12000, Jerusalem, Israel
Nutr Cancer; 3(1):20-26 1981

The effect of iron deficiency on tumor growth and host survival was studied in BALB/c mice with transplanted Plasma Cell-II tumors. Each experiment consisted of 60-120 mice into three groups: Group A was maintained on a commercial Purina diet; Group B received a diet of 50% milk powder and 45% corn flour supplemented with 5% oil and 1 mg CuCl2/100 g diet; Group C received the Group B diet supplemented with 200 mg FeCl3/100 g diet. Iron deprivation retarded the growth of weanling BALB/c mice but had no significant effect on the body wt of adult BALB/c mice. Well-formed tumor masses were palpable in greater than 90% of the animals at the site of inoculation within 20 days after injection of 4 x 10(6) tumor cells, and within 35 days after injection of 10(6) tumor cells. In most iron-deficient weanlings, the implanted tumors showed no increase in size from day 25 after inoculation. Iron deprivation of adult mice had no effect on tumor size. The survival of hosts fed on the Purina diet (Group A) was significantly shorter than that of iron-deficient tumor-bearing animals. No significant differences were noted in survival between iron-deficient tumor-bearing mice (Group B) and mice main-

tained on the same diet with iron supplementation (Group C). (22 Refs)

20. IN VITRO BONE MARROW CFU-C MYELOMA PATIENTS AND CELLULAR INTERACTIONS IN HAEMATOPOIESIS (MEETING ABSTRACT).

Giannoulis N, Osby E, Andersson B, Hadjisotiriou GD, Reizenstein P
Division of Haematology, Karolinska Hospital, Stockholm, Sweden
Sixth Meeting of the International Society of Haematology, European and African Division, August 30-September 4, 1981, Athens, Greece. Hellenic Society of Haematology 409 pp., 1981.

Because of the hematological findings in myeloma patients and of the cellular interactions in hematopoiesis we studied the bone marrow (BM) colony-forming units (CFUc) in 16 myeloma patients using the semi-solid agar culture technique. Conditioned medium prepared from the same myeloma patients was also tested for its in vitro effect on normal BM CFUc. The numbers of BM CFUc in the 16 myeloma patients were similar to those obtained from 12 healthy volunteers. A wide range of colony and cluster numbers was found in both groups. Medium conditioned from myeloma marrow cells caused an inhibition of normal BM CFUc ranging from 20 to 80%. These findings indicate that there is no decrease in the number of granulocyte progenitor cells in the bone marrow of myeloma patients and moreover it implies that malignant cells (plasma cells) may secrete factor(s) with an inhibitory effect on granulopoiesis. (no Refs)

21. STUDIES ON THE 'IN VITRO' PRODUCTION OF MONOCLONAL AND POLYCLONAL IMMUNOGLOBULINS BY PERIPHERAL BLOOD MONONUCLEAR CELLS IN HUMAN PLASMA CELL MYELOMA (MEETING ABSTRACT).

Peest D, Mellstedt H, Holm G, Pettersson D
Department of Clinical Immunology, Huddinge Hospital, Huddinge, W. Germany
Sixth Meeting of the International Society of Haematology, European and African Division, August 30-September 4, 1981, Athens, Greece. Hellenic Society of Haematology 409 pp., 1981.

The 'in vitro' monclonal and polyclonal immnouglobulin production of peripheral blood mononuclear cells was studied in human multiple myeloma (four IgG myelomas, one IgA myeloma and one patient with benign monoclonal gammopathy). Using an enzyme linked immunosorbent assay and anti-Idiotype sera it was possible to quantitate Ig amounts of cell culture supernatants and to distinguish clearly between monoclonal and polyclonal Ig of the same class. The patients cells showed remarkable lower Ig production than cells of healthy adults, varying with the patients state of health. Kinetics, protein synthesis inhibitio n, and estimation of cellular Ig from monoclonal Ig releasing cells revealed certain abnormalities: Spontaneous pokeweed mitogen (PWM) independent production of monclonal Ig and high levels of cellular Ig compared to the Ig levels in the culture medium. These abnormalities may give important informations about the role of the monclonal Ig secreting blood cells within the whole tumor cell clone. (no Refs)

22. MONOCLONAL ANTIBODIES AGAINST SURFACE ANTIGENS OF LARYNGEAL CARCINOMA CELLS.

Zenner HP
Universitatsklinik und Poliklinik fur Hals-, Nasen-, und Ohrenkranke, Kopfklinikum Wurzburg, D-8700 Wurzburg, W. Germany
Arch Otorhinolaryngol; 233(2):161-172 1981

Production of monoclonal antibodies against laryngeal carcinoma (LC) cells is reported. BALB/c mice were immunized with LC cells of line HLaC78 (1 x 10(6)-5 x 10(7) cells x 2 at a 6-wk interval) or with cell membranes (CM) from LC cells. Spleen cells were obtained 3 days after the second injection. Spleen cells were fused with mouse myeloma 653 cells to form antibody-producing cells capable of proliferation. A total of 1,882 clones of spleen cells were developed, including 1,102 from mice immunized with CM and 780 from mice immunized with intact cells (IC). Antibodies that bound to intact LC were produced by 73 clones, all from IC-immunized mice. Antibody from one clone was identified which bound malignant target cells, including two types of LC and two types of salivary gland tumor cells, but which did not bind normal fibrocytes, lymphocytes, or other normal human cell types, or nonhuman cells. The antibody, produced by hybridoma clone 1g6, was an IgG. Diagnostic potential of the IgG is described. (32 Refs) (In GER)

23. HUMAN HYBRIDOMAS FROM MALIGNANT GLIOMAS.

Sikora K, Alderson T, Phillips J, Watson JV
Ludwig Inst. Cancer Res., Hills Road, Cambridge, CB2 2QH, England
Lancet; 1(8262):11-14 1982

Intratumoral lymphocytes from 12 patients undergoing craniotomy for malignant glioma were fused with a specially derived human myeloma line LICR-LON-HMy2. Seventy one stable hybridomas were obtained from 5 of the 12 patients. Such hybridomas had a DNA content equal to the sum of that present in lymphocytes and the parent myeloma. The hybridoma supernatants contained human monoclonal immunoglobulins. Glioma-binding activity was detected in 7 out of the 71 supernatants. These results suggest that malignant gliomas contain a population of B lymphocytes which may be involved in host defense against the tumor. (Author abstract) (14 Refs)

24. DETECTION OF MELANOMA TUMOR ASSOCIATED ANTIGENS IN SERA BY ENZYME LINKED MONOCLONAL ANTIBODIES (MEETING ABSTRACT).

Hersey P, Schiltknecht E, Kemkemian H, McCarthy WH
No affiliation given
Clinical Oncology Society of Australia, November 24-17, 1981, Melbourne, Australia. The Society 70 pp., 1981.

An enzyme linked immunosorbent assay (ELIZA) was developed for the detection of melanoma antigens in unfractionated or small mw fractions (less than 100,000d) of sera from melanoma patients. Antibodies were from 4 hybrid murine myelomas that were reported to be relatively specific for melanoma and to react with a high proportion of melanoma cells. In studies on 21 melanoma patients and 25 patients with various malignancies antigen was detected in a high proportion (95%) of the melanoma patients but in only 16% of non-melanoma patients. The studies on the small mw fraction of sera yielded the best discrimination between melanoma and non-melanoma patients. The reaction of the 4 monoclonals varied with sera from different patients suggesting they were detecting different but overlapping antigenic determinants. Levels of antigen in sera became undetectable after surgical removal of localized melanoma and recurrence of melanoma in one patient was preceded by the appearance of antigen in the sera by several mo. These results suggest that existing monoclonal antibodies to melanoma antigens may be useful to monitor tumor growth in melanoma patients and justify more extensive evaluation for this purpose. (no Refs)

25. DETECTION OF HUMAN OSTEOSARCOMA-ASSOCIATED ANTIGEN(S) BY MONOCLONAL ANTIBODIES.

Hosoi S, NakamuraT, Higashi S, Yamamuro T, Toyama S, Shimomiya K, Mikawa H
Dept. Pediatrics, Univ. Kyoto, Sakyo-ku, Kyoto 606, Japan
Cancer Res; 42(2):654-659 1982

Hybrid cell lines have been derived from a fusion between mouse myeloma cells, NS1, and spleen cells from mice immunized with freshly resected osteosarcoma cells from an untreated patient. Of the 276 hybrids obtained, five secreted antibodies which bound to osteosarcoma tissues but not to autologous skin fibroblasts. The antibodies from three of these five hybrids, OST6, OST7, and OST15, reacted with all of five osteosarcoma tissues and with one chondrosarcoma tissue but not with other malignant or benign tumors. Tests of various normal tissues were negative, except for weak binding to a subpopulation of chondrocytes in articular cartilage. The reciprocal binding inhibition test showed that OST6, OST7, and OST15 antibodies were directed against different antigenic determinants. (Author abstract) (24 Refs)

26. METHODS FOR PRODUCTION OF MONOCLONAL ANTIBODIES WITH SPECIFICITY FOR HUMAN LUNG CANCER CELLS.

Minna JD, Cuttitta F, Rosen S, Bunn PA, Carney DN, Gazdar AF, Krasnow S
NCI-Veterans Admin. Branch, Div. Cancer Treatment, NCI, Washington, DC
In Vitro; 17(12):1058-1070 1981

We have developed a screening strategy and technology to produce monoclonal antibodies with specificity for human lung cancer cells. Mice and rats were immunized with well-characterized tissue culture lines of human small cell lung cancer (SCLC), mouse myeloma x spleen hybrids formed by the technique of Kohler and Milstein, and the resulting culture fluids were screened for antibody binding phenotype using a radioimmunoassay. To facilitate testing large numbers of culture fluids, a 96-well, microtiter based, re-usable, replicating device was designed. Using this, many hybridoma culture fluids were replica plated for antibody binding tests on a series of human target cell plates. Hybrids producing antibodies that reacted with the immunizing SCLC line and another independent SCLC line, but not with autologous B-lymphoblastoid cells derived from one of the patients, were identified, selected, and then repeatedly recloned using the same screening strategy. With this technology, hybridomas representing less than 0.5% of all hybrids generated could be isolated and stable antibody producing cultures derived. Such antibodies reacted with a panel of well-characterized SCLC lines and SCLC samples taken directly from patients but not with a variety of normal tissues. Using these antibodies we can demonstrate: tumor cell contamination of bone marrow specimens, marked heterogeneity of antigen expression on cells within individual SCLC lines and individual patients, and inhibition of clonal growth of SCLC lines in soft agarose assays. All of these findings have potential clinical and cell biologic application. (Author abstract) (50 Refs)

27. NATURAL ANTIBODIES AND MYELOMA PROTEINS SHARE SIMILAR ANTIBODY SPECIFICITIES (MEETING ABSTRACT).

Avrameas S, Guilbert B, Dighiero G
Unite d' Immunocytochimie, Institut Pasteur, Paris, France
Sixth Meeting of the International Society of Haematology, European and African Division, August 30-September 4, 1981, Athens, Greece. Hellenic Society of Haematology 409 pp., 1981.

The presence in the sera of various animal species of natural antibodies directed against various 'foreign' but also 'self' antigens is well established experimental fact. In the present work, we searched for the presence of natural antibodies directed against 9 ubiquitary antigens. To do so, the human sera from a pool of 800 donors and from 3 individual donors were run through tubulin, actin, thyroglobulin, myoglobin, fetuin, transferrin, albumin, cytochrome and collagen immunoadsorbants. Proteins were eluted from all the immunoadsorbants and were essentially composed of the 3 major Ig classes and albumin. The specificity of the isolated antibodies was studied using competitive and non-competitive immuno-assays. It was found that natural antibodies against all the antigens studied were present in the sera of normal humans. We presume that if these studies are extended to other antigens, naturally reacting antibodies to virtually all self antigens will be found in normal human serum. These results prompted us to searc h in the sera of patients with monoclonal gammapathies, paraproteins having natural antibody-like function. Among the 62 paraproteins studied for their receptivity with the 9 antigens mentioned above, 3 were shown to react with actin and one with tubulin. Most important, these 4 monoclonal immunoglobulins exhibited similar specificities to that found with natural antibodies. This seems to indicate that, at least for some patients, the monoclonal immunoglobulins produced may represent the expansion of a clone producing a natural antibody. (no Refs)

REVIEWS

28. MULTIPLE MYELOMA.

Cornwell GG
Section Hematology and Oncology, Dartmouth Medical Sch., Hanover, NH
Curr Ther; 28:333-336 1981

Supportive measures, management of direct complications, specific therapy, and new developments in multiple myeloma (MM) are discussed. The two most important goals for the patient with MM are ambulation and adequate hydration. Patients with serum Ca of 12 g/100 ml or greater should be treated as medical emergencies. Other complications are hyperuricemia, infection, pain associated with bone lesion, renal failure, pathologic fracture, neurologic deficit, hyperviscosity, and amyloidosis. Melphalan (MEL) or cyclophosphamide (CY), used as single agents, are equally effective in prolongation of survival. Carmustine (CAR) or lomustine every 6 wk, combined with an initial 6-wk tapering course of prednisone (PR), are equally effective in previously untreated patients. In most studies of untreated patients, combinations including doxorubicin (DOX) or procarbazine were superior to MEL and PR alone. A five-drug combination (vincristine, DOX, CAR, CY, MEL) resulted in significant objective remission in 87% of untreated patients. Radiation, tested in small groups of patients, has been ineffective. A small number of previously untreated and treated patients has shown response to daily doses of human leukocyte

interferon. Trials comparing interferon with standard therapy are being conducted. Culture techniques are being studied to determine effects of various chemotherapeutic agents on myeloma cells in vitro. (no Refs)

* U. S. GOVERNMENT PRINTING OFFICE : 1982—361-847/119

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DIAGNOSIS

1. JUSTIFIED SUSPICION OF MONOCLONAL GAMMOPATHY IN THE DIAGNOSIS OF INTERNAL DISEASES.

Hrncirova L, Machova L
II. vnitrni klinika, Lekarska fakulta UJEP, Jugoslavska 57, 613 00 Brno, Czechoslovakia
Vnitr Lek; 27(12):1145-1151 1981

Agar- and immuno-electrophoretic examinations were carried out in 292 patients with clinically suspected monoclonal gammopathy (MG) (Group I) and in 288 patients in whom MG was suspected on the basis of laboratory findings (Group II). MG was confirmed in Group I in 46/246 patients, in 25/83 patients with multiple myeloma, 0/1 with Waldenstrom's macroglobulinemia, 0.5 with leukemia, 2/7 with suspected Hodgkin's disease, 4/4 with suspected malignant tumors, 0.4 with generalized lymph node syndrome, 0.2 with m yelofibrosis, 0.6

HE 20. 3173/2:

with bone marrow depression, 0.5 with osteoporosis, 0.8 with splenomegaly, 2/2 with hemorrhagic diathesis, 0/18 with occult fever, 1/60 with systemic connective tissue disease, 2/9 with recurrent bronchopneumonia, 3/3 with chronic dyspeptic syndrome, and 7/75 with chronic active hepatitis or liver cirrhosis, In Group II, MG was confirmed in 59/288 patients: in 5/38 patients with anemia of unknown etiology, 18/158 with increased erythrocyte sedimentation rate, in 6/20 with dysproteinemia, 0/13 with hypogammaglobulinemia, and 30/59 with hypergammaglobulinemia. Multiple myeloma IgA was diagnosed in 16/105 patients, nonmyeloma IgA MG in 5, multiple myeloma IgG in 36, nonmyeloma IgG MG in 32, multiple myeloma IgG-IgA in 4, multiple myeloma IgG-BJL in 1, Waldenstrom's macroglobulinemia in 8 and other IgM MG in 3. (24 Refs) (In CZE)

2. SYSTEMIC AMYLOIDOSIS AND NON-HEMATOLOGIC MALIGNANCY IN A LARGE AUTOPSY SERIES.

Dictor M, Hasserius R
Inst. Pathology, Univ. Hosp., Lund, Sweden
Acta Pathol Microbiol Scand [A]; 89(6):411-416 1981

A series of 24,388 consecutive autopsies yielded 148 cases of amyloidosis, for which the associated diseases were tabulated. Thirteen solid primary malignancies were found in 11 patients, including 1 mucoepidermoid cancer of the parotid and 1 thymoma: 2 out of 11 had evidence of pyelonephritis. Five patients suffered from past or present renal adenocarcinoma, the most common carcinomatous cause of amyloidosis. Systemic amyloid deposits thus occurred in 2.1% of autopsied patients with renal carcinoma, but showed no obvious correlation with tumor stage or histologic type. Details are presented of an unusual case of hypernephroma producing a stable bronchial metastasis cuffed by nodular amyloid and dissociated by a lymphoid infiltrate containing plasma cells. The occurrence of systemic amyloidosis in non-hematologic malignancy thus appears to be a rare event, which, especially in the case of renal cancer, is assumed to be due to amyloid-fibril protein AA. (Author abstract) (12 Refs)

3. A STUDY OF AMYLOID ARTHROPATHY IN MULTIPLE MYELOMA.

Hickling P, Wilkins M, Newman GR, Pritchard MH, Jessop J, Whittaker J, Nuki G
Dept. Rheumatology, Welsh Natl. Sch. Medicine, Heath Park, Cardiff, Wales
Q J Med; 50(200):417-433 1981

Symptoms and clinical signs of arthropathy were present in 10/43 patients with multiple myeloma (MM). Classical osteoarthritis was present in 7/10 and amyloid arthropathy in 3/10. The patients with amyloid arthropathy were the only members of the group who had pure Bence-Jones MM (kappa in 1/3, lambda in 2/3). The first symptoms of arthropathy (3 mo-greater than 5.5 yr after the diagnosis of MM) were symmetrical polyarthritis of the small joints of the hands. Involvement of the knee and and shoulder joints developed later. All patients had the carpal tunnel syndrome. Soft tissue amyloidosis developed after the onset of the arthropathy; 2/3 patients showed generalized amyloidosis at death (7.5-9.75 yr after the diagnosis of MM). Analysis of synovial fluid cryoprecipitates showed no depression of complement components or specific light chain-containing immune complexes. Histochemical and ultrastructural examination of amyloid in the perichondrocytic lacunae, synovial fluid debris, synovium, and articular cartilage surfaces suggested that the chondrocytes and synovial macrophages may share a role in processing immunoglobulin components as a preliminary step in the formation of amyloid. Amyloid arthropathy occurs in about 5% of MM patients and may be primarily associated with pure Bence-Jones MM. The clinical picture can resemble rheumatoid arthritis, but the loss of function in the joints (especially the hands) of these patients seemed out of proportion to the relatively mild degree of abnormality apparent on examination. It is suggested that the combination of arthropathy and the carpal tunnel syndrome is a patient with MM may be a sign of amyloidosis. The diagnosis can be made by examination of Congo red-stained synovial fluid sediments under polarized light, even when no other clinical features of amyloidosis are present and the rectal biopsy is negative. (32 Refs)

4. INCOMPLETE FIBRIN FORMATION AND HIGHLY ELEVATED FACTOR XIII ACTIVITY IN MULTIPLE MYELOMA.

Klingemann HG, Egbring R, Havemann K
Medizinische Poliklinik der Universitat, Emile-Mannkopffstr. 1, D-3550 Marburg, W. Germany
Scand J Haematol; 27(4):253-262 1981

Bleeding is a common complication in patients suffering from multiple myeloma. In some cases a defect in fibrin formation has been suggested as one possible cause of hemorrhagic tendency. As shown in this investigation the defect in fibrin formation, ascertained using PAGE, is due to a lack of alpha-chain polymerization of fibrin monomers in 5/11 patients with IgG myeloma and in 2/5 patients with IgM paraproteinemia. No disturbed fibrin polymerization could be observed in IgA myeloma ($n = 6$). Factor XIII concentrations of subunit A and to a lesser extent of subunit S (Laurell technique) were highly elevated in all cases with regular fibrin formation. Comparable values were obtained by measuring the transamidase activity of factor XIII by incorporation of 14C-labeled putrescine into casein. Levels up to 600% of normal could be recorded. In contrast, all patients with a lack of alpha-chain polymerization had a factor XIII activity within the normal range. Addition of factor XIII concentrate to plasma from patients with defective fibrin formation led in 5/8 cases to a partial cross-linking of alpha-monomers. We conclude that in some cases paraproteins can inhibit the factor XIII and prevent its action on fibrin. (Author abstract) (23 Refs)

CLINICAL IMMUNOLOGY AND IMMUNOTHERAPY

5. DEFECTIVE MONOCYTE CHEMOTACTIC RESPONSIVENESS IN PATIENTS WITH MULTIPLE MYELOMA AND BENIGN MONOCLONAL GAMMOPATHY.

Dammacco F, Miglietta A, Ventura MT, Bonomo L
Patologia Medica II, Foliclinico, 70124-Bari, Italy
Clin Exp Immunol; 47(2):481-486 1982

The chemotactic responsiveness of peripheral blood monocytes was evaluated in three groups of subjects: 32 patients with multiple myeloma, 27 subjects with benign monoclonal gammopathy, and 64 normal controls. Monocyte chemotactic responsiveness was significantly depressed both in multiple myeloma patients (p less than 0.001) and in subjects with benign monoclonal gammopathy (p less than 0.001) as compared to that found in the control population. Although the re-

sults of chemotactic response obtained in multiple myeloma and in benign monoclonal gammopathy patients were largely overlapping, a significant difference was also found between the mean values of the two groups (p less than 0.025). The results support the hypothesis that myelomatosis, similarly to other neoplasms, may affect monocyte migratory activity thus hindering immunologically mediated destruction of tumor cells. (Author abstract) (22 Refs)

6. MONOCLONAL BLOOD LYMPHOCYTES IN BENIGN MONOCLONAL GAMMOPATHY AND MULTIPLE MYELOMA IN RELATION TO CLINICAL STAGE.

Pettersson D, Mellstedt H, Holm G, Bjorkholm M
Radiumhemmet, Karolinska Hosp., S-10401 Stockholm 60, Sweden
Scand J Haematol; 27(4):287-293 1981

Twenty patients with benign monoclonal gammopathy (BMG) have been studied for blood lymphocyte and subpopulations. Four patients had slightly decreased T-lymphocyte values. Total B-lymphocytes were within the normal range. In three BMG patients an abnormal ratio between chi- and lambda-bearing lymphocytes was detected indicating circulating monoclonal cells. Forty-one patients with untreated multiple myeloma have also been analyzed for blood monoclonal lymphoid cells using the chi:lambda-ratio. Fifty-four percent of the patients had monoclonal blood cells at diagnosis. The incidence and numbers of such cells increased with advanced clinical stage. Thus, it seems as if tumor volume is the main factor responsible for the appearance of monoclonal blood cells in multiple myeloma. (Author abstract) (23 Refs)

7. INCREASE IN THE NUMBER OF LYMPHOCYTES SECRETING IGG FOLLOWING BLOOD TRANSFUSION.

Shimizu K, Kitoh S
First Dept. Internal Medicine, Nagoya Univ. Sch. Medicine, 65 Tsuruma-Cho, Showa-Ku, Nagoya 466, Japan
Blood; 59(2):312-316 1982

A sequential change in the number of circulating immunoglobulin (Ig) secreting cells of each Ig class following blood transfusion was studied using a reverse hemolytic plaque assay. The subjects studied were in two main groups, immunologically normal individuals and patients with malignant lymphoma or multiple myeloma who are presumably, immune incompetent. A consistent increase in circulating IgG-secreting cells, along with either an earlier or simultaneous increase in IgM-secreting cells, was observed following blood transfusion in the immunologically normal individuals. An increase in IgA-secreting cells was also observed, but at a minimal magnitude. Such an increase was not apparent in patients with lymphoma or myeloma. The possible use of blood transfusion as a means of 'challenging and checking' for the state of immune responsiveness in vivo is discussed. (Author abstract) (9 Refs)

8. MONITORING OF A LONG SURVIVAL MYELOMA PATIENT.

Boccadoro M, Van Acker A, Carmagnola A, Conte F, Pileri A
Cattedra di Ematologia, Ospedale San Giovanni, Via Genova 3, 10126 Torino, Italia
Tumori; 67(6):571-573 1981

Monitoring with anti-idiotypic sera has been applied to identify tumoral cells in a myeloma patient still alive in complete remission 9 yr after diagnosis. Monoclonal plasma cells displayed a labeling index that decreased in complete remission below 1%. The great majority of B lymphocytes belonged to the tumoral clone even in complete remission and were therefore not affected by conventional chemotherapy. Some aspects of this myeloma patient are discussed in the light of these immunologic and kinetic findings. In addition, it is suggested that the therapeutic management of the complete remission should be re-examined, by considering a lymphocytolytic therapy. (Author abstract) (12 Refs)

CHEMOTHERAPY

9. CISPLATIN, BCNU, CYCLOPHOSPHAMIDE, AND PREDNISONE IN MULTIPLE MYELOMA.

Broun GO, Petruska PJ, Hiramoto RN, Cohen HJ
Div. Hematology and Oncology, St. Louis Univ. Sch. Medicine, 1325 S Grand Blvd., St. Louis, MO, 63104
Cancer Treat Rep; 66(2):237-242 1982

Using the MOPC 104E murine plasmacytoma model, Ghanta et al have shown major synergism when cisplatin was added to a treatment program with BCNU (carmustine) and cyclophosphamide (CTX). To evaluate possible synergism in the treatment of human multiple myeloma (MM), 23 evaluable patients who had relapsed with standard treatment were treated with cisplatin, BCNU, CTX, and prednisone. There were five good and four fair responses in this group of heavily pretreated patients. These included responses in four patients who had failed to respond to or had relapsed with BCNU, CTX, and prednisone therapy at higher doses than those used in this protocol, indicating that there is synergism from the addition of cisplatin in the treatment of human MM. Gastrointestinal toxicity was significant but acceptable. Transient renal and hematologic toxicity was also seen. The number of responses and the apparent synergism seen suggest that this combination of drugs should be studied as therapy for untreated patients with MM, especially those wi th poor prognostic features. (Author abstract) (10 Refs)

CASE REPORTS

10. COEXISTENT MULTIPLE MYELOMA AND PRIMARY HYPERPARATHYROIDISM.

Stone MJ, Lieberman ZH, Chakmakjian ZH, Matthews JL
Charles A. Sammons Cancer Center, Baylor Univ. Medical Center, 3500 Gaston Ave., Dallas, TX, 75246
JAMA; 247(6):823-824 1982

A patient with multiple myeloma and hypercalcemia responded to cytotoxic chemotherapy. However, hypercalcemia persisted. Because of the absence of lytic bone lesions, the presence of a low serum phosphate level, and a family history of possible primary hyperparathyroidism, the patient was evaluated for this disorder. Serum parathyroid hormone and urinary cyclic adenosine monophosphate levels were elevated. Exploration of the neck disclosed two enlarged parathyroid glands (1,850 mg and 210 mg), which were excised. After surgery, the patient's serum calcium levels remained normal for one year. Progressive myeloma bone disease developed that eventually resulted in recurrent hypercalcemia and death. Autopsy revealed only evidence of myeloma. (Author abstract) (9 Refs)

11. MYELOMATOSIS IN APLASTIC ANAEMIA - A TRUE ASSOCIATION OR FORTUITOUS OCCURRENCE?

Manoharan A, Horsley R, Pitney WR
St. George Hosp., Kogarah 2217, Australia
Pathology; 13(4):771-773 1981

A patient with aplastic anemia subsequently developed multiple myeloma. This unusual association may have been coincidental but a possible link is discussed. Should similar cases occur, it is important that they be documented, as more experimental and clinical evidence is necessary before lymphoid malignancies are related to bone marrow injury. (Author abstract) (8 Refs)

12. MULTIPLE MYELOMA COMPLICATING GAUCHER'S DISEASE.

Lamon JM, Lamon JM, Tavassoli M, Longmire R, Beutler E
Div. Hematology and Oncology, Scripps Clinic and Res. Foundation, La Jolla, CA, 92037
West J Med; 136(2):122-128 1982

A case report of this extremely rare condition was the topic of a panel discussion. The subject was a 66-yr-old Jewish female who had had the underlying disease for the least 40 years. The panel reviewed known cases and these associated topics: unexplained association of Gaucher's disease with immunoproliferative disorders, myeloma cell evaluation, normal chemotherapy for multiple myeloma and its contraindication by the complication of Gaucher's disease. (27 Refs)

13. SPECIFIC CUTANEOUS MANIFESTATIONS OF WALDENSTROM'S MACROGLOBULINAEMIA. A REPORT OF TWO CASES.

Mascaro JM, Montserrat E, Estrach T, Feliu E, Ferrando J, Castel T, Mallolas J, Rozman C
Dept. Dermatology, Hosp. Clinico y Provincial, Casanova 143, Barcelona-36, Spain
Br J Dermatol; 106(2):217-222 1982

Patients affected by Waldenstrom's macroglobulinemia may rarely present specific cutaneous manifestations. The violaceous plaques or tumors infiltrated by lymphoplasmocytoid cells, and the pink, translucent, shiny papules composed of deposits of hyaline monoclonal IgM possess definite clinicopathological characteristics that may permit the diagnosis before any other data are available. The immunopathological and ultrastructural features of these lesions are described. (Author abstract) (13 Refs)

14. COEXISTENT MULTIPLE MYELOMA AND PAGET'S DISEASE OF BONE.

Wong DF, Bobechko PE, Becker EJ, Howe GR
(c/o Bobechko) Dept. Radiology, Toronto General Hosp., 101 College St., Toronto, Ontario M5G 1L7, Canada
J Can Assoc Radiol; 32(4):251-253 1981

We found one patient with coexistent multiple myeloma and Paget's disease of bone in a series of 50 consecutive patients with myeloma who had had skeletal surveys between 1972 and 1979. Only 43 examples of these diseases coexisting have been previously cited. The patient reported here had extensive radiographic changes of Paget's disease and multiple myeloma with the disease involving the same bones. A second patient diagnosed in 1949 is also briefly described. Studies to date are statistically inadequate to determine if a true association between Paget's disease and multiple myeloma exists. We estimate that as many as 780 patients with myeloma and controls may be required to answer this question if the presence of Paget's disease at least doubles the risk of subsequent myeloma. (Author abstract) (7 Refs)

SELECTED PRE-CLINICAL STUDIES

15. ULTRASTRUCTURAL ANALYSIS OF MEMBRANE-BOUND POLYSOMES IN HUMAN MYELOMA CELLS.

Kitani T, Yonezawa T, Imanaka T, Hiraoka A, Nasu T
Div. Internal Medicine, Dept. Clinical Res., Res. Inst. for Microbial Diseases, Osaka Univ. 3-1, Yamada-oka, Suitashi, Osaka 565, Japan
Blut; 44(1):51-63 1982

Counts of ribosomes were determined in membrane-bound polysomes of 75 patients with different M-protein compositions (44 IgG-, 14 IgA-, 5 IgD-, 2 IgE-myelomas, 1 macroglobulinemia, 9 BJP myeloma). Ultrathin sections (about 50 nanometer) were cut tangentially and were examined by electron microscopy. For each patient 10-15 micrographs (magnification x 10,000) were inspected and 100-200 membrane-bound polysomes of perfect shape were used for the ribosome counts. The curves of ribosome distribution (up to 21 ribosomes) showed two peaks for IgM, a high peak at 7 and a lower peak at 17-18 ribosomes. Peaks were observed at 7 and 13 ribosomes for IgA-, IgD- and IgE myeloma and macroglobulinemia. BJP myeloma showed a sharp peak only at 7 ribosomes. The results suggest that BJP myeloma has only small polysomes participating in light (L) chain synthesis while the other myelomas have large and small polysomes participating in heavy (H)- and L-chain synthesis, respectively. A similar analysis of marrow from a liver cirrhosis pat ient with marked reactive plasmacytosis showed sharp peaks at 7 and 17 ribosomes, similar to that obtained in the IgG myeloma patients. The present findings in the myeloma patients can be accounted for by structural relationship between immunoglobulins and Bence Jones proteins. The relationship of polysome size to L- and H-chain globulins is discussed. (13 Refs)

16. PROTON NMR STUDY OF THE BINDING OF CONCANAVALIN A ON MYELOMA PLASMA MEMBRANES.

Tellier C, Curtet C, Poignant S, Godard A, Aubry J
(c/o Poignant) Laboratoire de Chimie Organique Physique, CNRS ERA No. 315, Faculte des Sciences, 44072 Nantes Cedex, France
Biochem Biophys Res Commun; 104(1):113-120 1982

Lipid extracts were prepared from the plasma membranes of MF2S cells derived from the murine plasmocytoma MOPC 173, grown as ascites in BALB/c mice. Concanavalin A (Con A) was preincubated 30 min with two different purified membrane samples at 37 C in nuclear magnetic resonance (NMR) spectroscopy vessels and analyzed. One of the two membrane fractions had a modified NMR spectrum after Con A treatment. Con A:lipid binding interactions are discussed. (15 Refs)

17. HUMAN MONOCLONAL IGM WITH AUTOANTIBODY ACTIVITY AGAINST INTERMEDIATE FILAMENTS.

Dellagi K, Brouet JC, Perreau J, Paulin D
(c/o Paulin) Departement de Biologie Moleculaire, Institut Pasteur, et Universite Paris VII, 25 Rue du Dr. Roux, 75015 Paris, France
Proc Natl Acad Sci USA; 79(2):446-450 1982

Monoclonal IgMs from two patients with Waldenstrom macroglobulinemia were found to react with intermediate filaments. This was shown by (a) immunostaining of various tissues and cultured cells and (b) immunological characterization of the reactive antigen after blotting of polypeptides separated from total cell extracts by gel electrophoresis or purified intermediate filaments on nitrocellulose sheets. One monoclonal IgM had an activity directed only against vimentin, whereas the other reacted with four different classes of intermediate filaments-vimentin, desmin, glial fibrillary protein, and keratins. All of the reactivity of the latter IgM was absorbed by purified vimentin, suggesting that different classes of proteins of intermediate filaments share common antigenic determinant(s). The significance of such autoantibody activity of human monoclonal IgM is discussed in the light of the startling frequency of IgM anti-intermediate filaments antibodies in various diseases. (Author abstract) (32 Refs)

18. ANALYSIS OF IMMUNOGLOBULIN MRNA IN MURINE MYELOMA CELL VARIANTS DEFECTIVE IN THE SYNTHESIS OF THE LIGHT OR HEAVY POLYPEPTIDE CHAINS.

Wallach M, Ishay-Michaeli R, Givol D, Laskov R
(c/o Laskov) Hubert H. Humphrey Center Experimental Medicine Cancer Res., Hebrew Univ.-Hadassah Medical Sch., Jerusalem, Israel
J Immunol; 128(2):684-690 1982

The immunoglobulin (Ig) mRNA species in spontaneously arisen myeloma cell variants, which lose the ability to synthesize the Ig heavy and/or light chains, were analyzed using the RNA blotting technique. Nick-translated recombinant plasmid clones containing kappa- and gamma-chain sequences were used as hybridization probes. It was found that the MPC 11 clone 4T00.1L1 and the MOPC 21 clone NSI, which are known to produce small quantities of the gamma2b and gamma1 heavy chains, respectively, contained correspondingly small amounts of gamma-mRNA molecules; although the gamma-mRNA of clone 4T00.1L1 was of normal size (1.9 kilo bases [kb]), the gamma-mRNA of clone NSI was of a smaller size (1.3 kb). Reduced quantities of a smaller sized gamma heavy chain mRNA were also found in the MPC 11 clone 66.2 (1.7 kb) and in MOPC 21 clones P3NP (1.7 kb) and 653 (1.7 kb), which do not produce detectable amounts of gamma heavy chains. The only nonproducer clone that seemed to be completely devoid of the gamma-mRNA was clone NP2 (MPC 11). With regard to the kappa-mRNA, the nonproducer MOPC 21 variants P3NP and 653 were found to contain appreciable amounts of smaller or normal-sized kappa-mRNA, respectively. In contrast, the MPC 11 nonproducer clone NP2 did not contain detectable levels of the full-length 1.2 kb kappa-mRNA, even though it did produce the 0.8 kb kappa-mRNA fragment, which is known to be present in all the MPC 11 clones. It would thus appear that most of the myeloma cell variants that lost the ability to produce Ig chains contain reduced to normal quantities of smaller or normal-sized Ig mRNA molecules. These findings indicate that in many of these mutants the respective Ig genes are not fully deleted. (Author abstract) (45 Refs)

19. TUMOR-SPECIFIC IMMUNITY INDUCED BY SOMATIC HYBRIDS. III. PERSISTENCE OF ADOPTIVELY TRANSFERRED IMMUNITY SPECIFIC FOR TEPC-15 PLASMACYTOMA IN NORMAL BALB/C MICE.

Kim BS
Dept. Microbiology-Immunology, Cancer Center, Medical and Dental Sch., Northwestern Univ., Chicago, IL, 60611
Cell Immunol; 65(2):373-379 1981

Immunity against TEPC-15 tumor cells was induced in BALB/c mice by injecting semi-allogeneic hybrid cells derived from fusion of TEPC-15 tumor cells with LM(TK(-)) cells of the C3H origin. Adoptive transfer of spleen cells from the immune mice into normal BALB/c recipients rendered them free from tumors following tumor challenge; the recipients were most significantly protected from the tumor when tumor cells were injected 7-14 days after the adoptive transfer of immune cells. Such immunity following adoptive transfer appeared to persist in the recipients for at least 60 days. Moreover, the tumor-specific immunity was consecutively transferable (more than 9 passages) into normal BALB/c recipients by serially passing spleen cells from the recipients every 14 days without further stimulation with the hyb rid cells or inactivated TEPC-15 tumor cells. Such consecutive transfer of the immune spleen cells induced splenomegaly in the recipients: a two- to five-fold increase over normal spleen cell recipients. The ability of spleen cells to transfer immunity, but not splenomegaly, was abrogated by treatment with mitomycin C. These results suggest that proliferation of donor cells is necessary to transfer immunity, and that splenomegaly alone does not manifest such immunity in the recipients. (Author abstract) (23 Refs)

20. EFFECT OF ESTRADIOL AND DEGREE OF CELL DIFFERENTIATION ON HUMAN MELANOMA SUSCEPTIBILITY TO KILLING BY MONOCLONAL ANTIBODIES.

Hakim AA
Dept. Oral Diagnosis, Coll. Dentistry and Basical Medical Sciences, Univ. Illinois, 180 Longwood Drive, Kankakee, IL, 60901
Immunol Lett; 4(1):59-64 1982

The relationship of antigenic determinants of melanotic and amelanotic human malignant melanoma cells to responsiveness to estradiol (ES) was studied. Cultures grown in the absence and presence of ES were used to develop various cell lines: a non-responsive melanotic (E-M+ShA) was derived from ES-responsive melanotic (E+M+ShA) and an ES-responsive amelanotic (E+M-SR) was derived from ES-non-responsive amelanotic (E-M-SR). Cellular responsiveness to hormone was determined by incubation with insulin, with addition of (3H)thymidine after 72 hr. Spleen lymphocytes from mice pre-immunized with E+M+ShA, E-M+ShA, E-M-SR, and E+M-SR were fused with murine non-producer myeloma cells to obtain mouse-mouse hybridoma cultures synthesizing monoclonal antibodies against human malignant melanoma. Complement-dependent cytotoxic activity of the monoclonal antibodies varied from one hybridoma to another. Results indicate that the antigenic determinants of melanoma cells vary from one cell line to another; efficiency of complement-mediated killing is a function of responsiveness to estradiol and degree of melanogenesis. (37 Refs)

21. DEVELOPMENT OF A MONOCLONAL ANTIBODY AGAINST A TUMOR-ASSOCIATED ANTIGEN.

Peng WW, Bressler JP, Tiffany-Castiglioni E, De Vellis J
Lab. Nuclear Medicine and Radiation Biology, Univ. California, Los Angeles, CA, 90024
Science; 215(4536):1102-1104 1982

A monoclonal antibody-producing hybrid cell line was obtained by fusing mouse myeloma cells with spleen cells from a mouse immunized with C6 glioma cells. This antibody binds to a specific cell-surface antigen that is present on C6 rat glioma cells, transformed astrocytes and oligodendrocytes, and a human glioma cell line but is absent on a normal glial cell line, fibroblasts, and primary cultures of astrocytes and oligodendrocytes. The antigen also appears on tumor tissue of transformed oligodendrocytes but not on normal brain tissue. (Author abstract) (18 Refs)

REVIEWS

22. TREATMENT OF MULTIPLE MYELOMA.

Woodruff R
Dept. Hematology, Medical Oncology Unit, Austin Hosp., Heidelberg, 3084, Victoria, Australia
Cancer Treat Rev; 8(4):225-270 1981

The last 20 yr have seen major advances in the treatment of multiple myeloma (MM). Whilst these improvements have been largely attributed to the development of effective chemotherapy, a major contribution has also been made by our ability to recognize and treat complications of the disease which in the past were major causes of early mortality and morbidity. The first part of this review examines the prognostic factors and the more recently developed staging system which are important in treatment planning and in the interpretation of the results of chemotherapy. Special mention is made of several uncommon subtypes of MM, such as indolent myeloma and plasma cell leukemia, for which a different therapeutic approach is indicated. This is followed by a discussion of symptomatic care and treatment of those disease complications where recent advances in our knowledge and therapy have led to significant improvements in the clinical management of MM. The main part of this review presents a detailed examination of the results of chemotherapy in MM, including the use of hormonal agents. The results of continued maintenance treatment are discussed in the context of new information concerning the cellular kinetics of the remission phase. Finally, immunotherapy, therapy with interferon and novel radiotherapeutic approaches are briefly reviewed. (Author abstract) (226 Refs)

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CLINICAL EVALUATION AND TREATMENT OF MULTIPLE MYELOMA AND OTHER GAMMOPATHIES

SERIES CT13 No. 82/08

AUGUST, 1982

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DIAGNOSIS

1. RADIOLOGICAL AND SCINTISCAN DIAGNOSIS AND FOLLOW-UP IN PLASMACYTOMA.

Brassow F, Crone-Munzebrock W
Radiologische Klinik, Universitatskrankenhaus, Hamburg-Eppendorf, Martinistrasse 52, 2000 Hamburg 20, W. Germany
Roentgenblaetter; 35(2):49-53 1982

Results of conventional x-ray (CXR) and scintigraphy (SG) of 32 patients (22 men and 10 women, 54-70 yr old) with bone involvement by plasmacytoma were compared. Single bone lesions were found in 6 patients and multiple lesions in 26 patients. SG was performed 2-4 hr after iv injection of 10-20 mCi radionuclide containing 99mTc. All patients received high-voltage therapy for at least one lesion. CXR and SG were repeated 3-6 mo after irradiation. SG detected accumulations of tracer in 85% of lesions detected by CXR; the extent of 30% of these lesions was underestimated by SG SG failed to detect

HE 20.3173/2:

15% of lesions detected by CXR. Fractures were detected in 37 cases by CXR. SG indicated extreme accumulations of tracer in only eight fractures and did not indicate any abnormality in six fractures. Of 12 fractures detected by CXR, SG indicated distinct increases in tracer activity in 8 cases and slight increases in 4 cases. In 32 patients with a total of 37 lesions treated by high-voltage therapy, CXR did not detect changes in the irradiated field. SG showed reductions in tracer activity, indicating tumor regression in 34 lesions; increases in tracer activity, indicating tumor progression, were detected in 3 patients. New occurrences of bone lesions were detected in 14 cases by SG and confirmed by CXR. Five new lesions were detected by CXR but not by SG. SG evidently cannot replace CXR for diagnosis of bone lesions resulting from plasmocytoma, but is of value in monitoring response to therapy. (9 Refs) (In GER)

2. FLOW CYTOMETRIC ANALYSIS OF DNA CONTENT OF BONE MARROW CELLS IN PATIENTS WITH PLASMA CELL MYELOMA: CLINICAL IMPLICATIONS.

Bunn PA, Krasnow S, Makuch RW, Schlam ML, Schechter GP
NCI-Navy Medical Oncology Branch, Natl. Naval Medical Center, Bestheda, MD, 20014
Blood; 59(3):528-535 1982

DNA content analysis by flow cytometry was performed in 32 patients with plasma cell myeloma and 3 patients with Waldenstrom's macroglobulinemia to determine the biologic and potential clinical usefulness of this technique. Hyperdiploid tumor DNA content was found in 23 myeloma patients (72%) during the course of illness, including 16/28 at presentation, but in none of 3 patients with Waldenstrom's macroglobulinemia. There was no significant association of aneuploidy in myeloma patients with age, sex, race, or M-protein class. Myeloma patients with aneuploid tumor cells were more likely to have advanced stage ($p = 0.032$) than patients with diploid plasma cells, and all patients with renal failure had aneuploid tumors. Pretreatment factors significantly associated with survival included stage ($p = 0.01$), serum creatinine ($p = 0.003$), and tumor DNA content ($p = 0.005$). Multivariate analysis using the Cox life table regression procedure indicated that the significant relation of tumor DNA content with survival remained after adjusting for stage (p less than 0.005). Myeloma patients with diploid tumors at diagnosis frequently had aneuploid plasma cells at the time of relapse, indicating a possible relationship of chromosomal alterations in the tumor to clinical drug resistance. We conclude that aneuploid tumor cells at the time of diagnosis of myeloma are of independent prognostic significance, and the development of aneuploidy is a frequent occurre nce at clinical relapse, suggesting the changes in DNA content are of biologic and clinical significance. (Author abstract) (29 Refs)

3. 'IDIOPATHIC' BENCE JONES PROTEINURIA. LONG-TERM FOLLOW-UP IN SEVEN PATIENTS.

Kyle RA, Greipp PR
Div. Hematology, Mayo Clinic, Rochester, MN, 55905
N Engl J Med; 306(10):564-567 1982

Seven patients (all men, 42-76 yr old, median age 56 yr) had idiopathic Bence Jones proteinuria (excretion of more than 1.0 g/24 hr) and no anemia, lytic bone lesions, hypercalcemia, renal insufficiency, excessive plasmacytosis, or other manifestations of multiple myeloma, amyloidosis, or lymphoproliferative diseases. Ultimately, three patients acquired symptomatic multiple myeloma 8.8-21.1 yr later. One of these was associated with systemic amyloidosis. One patient had asymptomatic myeloma and was not treated. One patient probably had a slowly evolving multiple myeloma but died at the age of 76 without overt multiple myeloma. Two patients had benign Bence Jones proteinuria after a follow-up period of 7.7-12 yr, and one had an extensive squamous-cell carcinoma involving the mediastinum and lungs. The percentage of plasma cells taking up tritiated thymidine was low in all cases. All three patients with lambda Bence Jones proteinuria had multiple myeloma, while the four patients with kappa chains had benign Bence Jones proteinuria, evolving multiple myeloma, or multiple myeloma with amyloidosis. Three patients excreted large amounts of Bence Jones protein without much change over a long period of time. Chemotherapy should not be given until symptomatic myeloma develops. Patients with idiopathic Bence Jones proteinuria should be kept under observation indefinitely since multiple myeloma and/or amyloidosis may develop. (24 Refs)

4. BENCE JONES PROTEINS: MALIGNANT OR BENIGN?

Solomon A
Center Health Sciences, Knoxville Unit, Coll. Medicine, Univ. Tennessee, Knoxville, TN, 37920
N Engl J Med; 306(10):605-607 1982

Whether benign monoclonal gammopathies are truly benign or presage the eventual development of a plasma-cell/lymphocytic neoplasm or amyloidosis is discussed. The transition from benign to malignant gammopathy has been reported in patients with monoclonal serum immunoglobulins. At least 60-80% of patients with multiple myeloma have Bence Jones proteinuria; in approx 20% of patients, Bence Jones proteins (BJP) may be the sole monoclonal immunoglobulin formed by the malignant plasma cell. Response or lack of response to chemotherapy can be documented by measurement of daily excretion of BJP. Appearance of BJ proteinuria in patients with myeloma usually signifies a transition to a more aggressive form of disease. BJP themselves are probably malignant entities with pathophysiologic effects, the most important of which are those on the kidney. Renal dysfunction in patients with BJ proteinuria may appear as proximal or distal tubular effects, nephrotic syndrome, or the development of azotemia. BJP are indicators of the primary or myeloma-associated form of amyloidosis. A poorer prognosis is associated with patients with lambda type of BJP than those with kappa type. Chemotherapy is recommended for symptomatic myeloma patients with BJP in their plasma or urine. Caution should be exercised for asymptomatic patients with BJP because of the toxicity and potential mutagenic of the drugs used. (15 Refs)

5. AMYLOID A IN SYSTEMIC AMYLOIDOSIS ASSOCIATED WITH CANCER.

Husby G, Marhaug G, Sletten K
Dept. Rheumatology, Inst. Clinical Medicine, Univ. Tromso, Tromso, Norway
Cancer Res; 42(4):1600-1603 1982

Amyloid fibrils from two cases of cancer-associated, systemic amyloidosis with renal cell carcinoma and mesothelioma as the respective underlying disorders were studied. The immunochemical studies suggested strongly that amyloid A comprised a principal fibril component in both cases of cancer-associated amyloidosis. This was definitely proven by amino acid sequence analyses, which revealed structural homology between a purified subcomponent of the amyloid fibrils from both of the two cases of cancer-associated amyloidosis and previously sequenced amyloid A proteins. The chemical composition of the amyloid fibrils from systemic amyloidosis associated with cancer thus corresponded to that seen in amyloidosis reactive

to inflammatory diseases and Hodgkin's disease. Amyloid proteins of immunoglobulin light chain type, which are found associated with myelomatosis, macroglobulinemia, and idiopathic (primary) amyloidosis, were not found in the two amyloid preparations. Renal cell carcinoma appears to be an effective stimulator of amyloid formation, while only one case of amyloidosis associated with mesothelioma has been reported previously. (Author abstract) (33 Refs)

CLINICAL IMMUNOLOGY AND IMMUNOTHERAPY

6. IDIOTYPIC PERIPHERAL BLOOD LYMPHOCYTES IN MONOCLONAL GAMMOPATHY.

Bast EJ, Van Camp B, Reynaert P, Wiringa G, Ballieux RE
Dept. Clinical Immunology, Univ. Hosp., P.O. Box 16250, 3500 CG Utrecht, The Netherlands
Clin Exp Immunol; 47(3):677-682 1982

Using two sets of anti-idiotypic antibody reagents (from guinea-pig and rabbit origin), idiotypic peripheral blood lymphocytes (PBL) could be shown in multiple myeloma patients in relapse, but not in remission. In patients having the benign form of monoclonal gammopathy, idiotypic lymphocytes were lacking except in some patients which were depicted as a 'high risk' group, by a multivariate rating system. If present, idiotypic lymphocytes accounted for 1-4% of PBL. (Author abstract) (30 Refs)

CHEMOTHERAPY

7. MULTIPLE MYELOMA RESISTANT TO MELPHALAN: TREATMENT WITH DOXORUBICIN, CYCLOPHOSPHAMIDE, CARMUSTINE (BCNU), AND PREDNISONE.

Kyle RA, Pajak RF, Henderson ES, Nawabi IU, Brunner K, Henry PH, McIntyre OR, Holland JF
Hematology and Internal Medicine, Mayo Clinic, Rochester, MN, 55901
Cancer Treat Rep; 66(3):451-456 1982

Sixty-five patients with multiple myeloma resistant to melphalan were randomized to receive cyclophosphamide, doxorubicin (Adriamycin), and prednisone (CAP) (30 patients) or carmustine (BCNU), doxorubicin, and prednisone (BAP) (35 patients). Objective responses occurred in two patients in the CAP group and in seven in the BAP group. Indirect responses were noted in seven additional patients in the CAP group and in six additional patients in the BAP group. Toxic effects consisted mainly of leukopenia and thrombocytopenia. Median survival did not differ between the two treatment groups (CAP, 8.4 mo; BAP, 7.7). Objective responders had a longer survival than nonresponders (14.5 vs 7.7 mo). (Author abstract) (24 Refs)

8. INFLUENCE OF RENAL FAILURE ON MYELOSUPPRESSIVE EFFECTS OF MELPHALAN: CANCER AND LEUKEMIA GROUP B EXPERIENCE.

Cornwell GG, Pajak TF, McIntyre OR, Kochwa S, Dosik H
Dept. Medicine, Dartmouth-Hitchcock Medical Center, Hanover, NH, 03755
Cancer Treat Rep; 66(3):475-481 1982

The influence of renal insufficiency on melphalan-induced myelosuppression was examined during the initial 10 wk of treatment in 295 patients with multiple myeloma. Patients were randomized to receive either oral melphalan (0.15 mg/kg/day for 7 days, followed by 0.05 mg/kg/day after recovery for the wbc count nadir) or iv melphalan (16 mg/m2 every 2 wk for four doses, followed by a single dose every 4 wk). All patients received a 6-wk tapering course of prednisone. Patients with renal insufficiency (BUN greater than or equal to 30 mg/100 ml) had a significantly higher frequency of severe leukopenia (less than or equal to 1,000 cells/mm3) following iv melphalan than did patients with normal renal function (50% vs 15%, respectively; $p = 0.007$). The latter effect resulted in an increased frequency of drug-related deaths secondary to infection. The frequency of severe thrombocytopenia (less than or equal to 25,000 cells/mm3) was also greater in patients with renal failure following iv melphalan therapy. Reduction of iv melphalan dose to 50% in patients with elevated BUN reduced the frequency of these complications to levels that were not significantly different from those observed in patients with normal renal function. The frequency of severe myelosuppression was independent of renal function in patients receiving oral melphalan. Possible explanations for these findings are discussed. (Author abstract) (5 Refs)

9. MELPHALAN-RELATED LEUKEMIA IN MULTIPLE MYELOMA.

Wahlin A, Roos G, Rudolphi O, Holm J
A. Wahlin, M.D., Dept. Internal Medicine, Univ. Hosital, S-901 85 Umea, Sweden
Acta Med Scand; 211(3):203-208 1982

Five patients with multiple myeloma ending in acute leukemia are described. The preleukemic phase was characterized by anemia, leukopenia and/or thrombocytopenia. The incidence of acute leukemia in myeloma was calculated to be 6%. Melphalan therapy for more than 2 years increased the incidence to 14%. All patients who developed leukemia had received a total melphalan dose of at least 1,000 mg. (Author abstract) (18 Refs)

RADIOTHERAPY

10. WHOLE BONE MARROW IRRADIATION FOR THE TREATMENT OF MULTIPLE MYELOMA.

Coleman M, Saletan S, Wolf D, Nisce L, Wasser J, McIntyre OR, Tulloh M
Oncology Section, Div. Hematology-Oncology, Dept. Medicine, New York Hosp.-Cornell Medical Center, 525 East 68th St., New York, NY, 10021
Cancer; 49(7):1328-1333 1982

Nine patients with multiple myeloma were treated with whole bone marrow irradiation. Six had heavily pretreated disease refractory to chemotherapy. Three had stable disease lightly pretreated by chemotherapy. A modification of the

'three and two' total nodal radiation technique was employed. Although varying and often severe treatment related cytopenia occurred, infectious complications, clinical bleeding, and non-hematologic complications were minimal. Five of nine patients showed a decrease in monoclonal protein components, and one showed an increase during treatment. These preliminary results indicate that a reduction of tumor cell burden may occur in patients following whole bone marrow irradiation and that the technique is feasible. Whole bone marrow irradiation combined with chemotherapy represents a new conceptual therapeutic approach for multiple myeloma. (Author abstract) (15 Refs)

SUPPORTIVE CARE

11. CHANGING PATTERNS OF INFECTIONS IN PATIENTS WITH MULTIPLE MYELOMA.

Shaikh BS, Lombard RM, Appelbaum PC, Bentz MS
Dept. Medicine (Div. Hematology), Milton S. Hershey Medical Center, Pennsylvania State Univ., Hershey, PA
Oncology; 39(2):78-82 1982

A total of 59 infections were encountered in 29/46 patients with multiple myeloma (MM). Most infections arose in the urinary tract (31%), respiratory tract (29%), followed by blood (12%), oropharynx (12%), skin and soft tissue (7%). Gram-negative bacilli were identified in 51% of infections, most common being Enterobacteriaceae and Hemophilus influenzae. Gram-positive organisms were responsible for 7% of infections. 24% of patients with urinary tract infections had signs of cord compression. Absolute lymphopenia was common, and was seen in 65% of patients with urinary infections, 75% of respiratory infections, and 86% of septicemic patients. In contrast, granulocytopenia was mainly observed in patients with septicemia (71%), followed by those with respiratory infections (31%). All patients were on cytotoxic chemotherapy, and m ost were hypoglobulinemic. About one third of septicemias, and one half of urinary and respiratory infections, respectively, were hospital-acquired. Results indicate that the current pattern of infections in MM seems to favor gram-negative organisms. The role of predisposing factors in the pathogenesis of infections in these patients is discussed. (Author abstract) (16 Refs)

CASE REPORTS

12. BENIGN MONOCLONAL GAMMOPATHY.

Hickman S, Avioli LV
Jewish Hosp. St Louis, 216 S. Kingshighway, P.O. Box 14109, St Louis, MO, 63178
Arch Intern Med; 142(2):349-351 1982

Benign monoclonal gammopathy (BMG) is discussed in a 73-yr-old man referred for evaluation of hyperglobulinemia and a 63-yr-old women referred for evaluation of a paraprotein. A definite diagnosis of multiple myeloma (MM) could not be established in either of these patients. Specific recommendations for their subsequent follow-up were made. The distinction between MM and BMG is important both prognostically and therapeutically but the diagnosis may be difficult to establish in some patients. (8 Refs)

13. IGE MYELOMA. REPORT OF A NEW CASE AND REVIEW OF THE LITERATURE.

Saia P, Tonutti E, Ruscio M, Colle R, Antonutto G, Falconieri G
via S. Maria C. di Rosa, 6, Udine 33100, Italy
Haematologica (Pavia); 66(6):787-795 1981

IgE myeloma is reported in a 69-yr-old woman admitted to the hospital with lower back pain, anorexia, weight loss, and in the days prior to admission, nausea and vomiting. A satisfactory response to chemotherapy was observed. A substantial reduction of the amount of serum IgE and of urinary Bence-Jones protein, improvement of anemia and thrombocytopenia, and disappearance of pain was noted. IgE myeloma according to available data does not appear to differ significantly from multiple myeloma, except in the frequent occurring, plasma cell leukemia. (24 Refs)

14. CENTRAL NERVOUS SYSTEM AMYLOID PRESENTING AS A MASS LESION. REPORT OF TWO CASES.

Townsend JJ, Tomiyasu U, MacKay A, Wilson CB
Dept. Pathology, Univ. California San Francisco Medical Center, San Francisco, CA, 94143
J Neurosurg; 56(3):439-442 1982

Amyloidomas of the central nervous system are rare. Two cases involving middle-aged patients with neurological symptoms are presented. Massive focal accumulations of amyloid in the cerebral hemispheres were confirmed pathologically. (Author abstract) (23 Refs)

15. ENDOBRONCHIAL METASTATIC PLASMACYTOMA.

Tenholder MF, Scialla SJ, Weisbaum G
Pulmonary Disease Service, Dwight David Eisenhower Army Medical Center, Fort Gordon, GA, 30905
Cancer; 49(7):1465-1468 1982

Plasmacytomas are rare tumors and an endobronchial presentation has not been previously described. A 64-year-old white woman with metastatic involvement by plasmacytoma is presented . A review of the literature indicates the difficulty in distinguishing this lesion from benign plasma cell tumors of the lung and the prolonged follow-up often necessary to reveal metastatic behavior. Careful observation in this case led to the demonstration of metastatic lung and endobronchial lesions without the development of abnormal proteinuria or overt myeloma. The literature would suggest a key role for radiation therapy in treatment. The role of chemotherapy, remains to be defined. (Author abstract) (5 Refs)

16. AN UNUSUAL CASE OF MYELOMA: NON-SECRETORY IGD-KAPPA WITH DE-DIFFERENTIATION TO KAPPA MYELOMA EVOLVING FROM SOLITARY PLASMOCYTOMA.

Nelis GF
Dept. Internal Medicine, Sophia-Ziekenhuis, Zwolle, The Netherlands
Acta Med Scand; 211(1/2):141-144 1982

The present report concerns a patient with 'non-secretory' IgD-kappa myeloma with two separate clones of myeloma cells: one secreting IgD-kappa and one producing but not secreting kappa light chains. The second clone is thought to be derived from the first by de-differentiation. Before the diagnosis of myeloma was made, the patient was considered to have a solitary plasmocytoma. (Author abst) (44 Refs)

17. MULTIPLE CRANIAL NERVE PALSIES AS THE PRESENTING FEATURE OF MENINGEAL MYELOMATOSIS.

Woodruff RK, Ireton HJ
Dept. Haematology, Austin Hosp., Heidelberg 3084, Victoria, Australia
Cancer; 49(8):1710-1712 1982

The case of a 69-yr-old man with IgGK myeloma in whom meningeal myelomatosis with multiple cranial nerve palsies developed, is reported. Review of previously reported cases of clinically apparent meningeal myelomatosis indicates this rare complication frequently presents with cranial nerve palsies; currently available treatment is ineffective. (Author abstract) (16 Refs)

SELECTED REPORTS ON ETIOLOGY AND EPIDEMIOLOGY

18. FAMILIAL MULTIPLE MYELOMA. A REVIEW OF THIRTY-SEVEN FAMILIES.

Shoenfeld Y, Shaklai M, Berliner S, Gallant LA, Pinkhas J
Dept. Medicine 'D', Tel Aviv Univ. Sackler Sch. Medicine, Beilinson Medical Center, 49100 Petah Tiqva, Israel
Postgrad Med J; 58(675):12-16 1982

The review of the pertinent literature disclosed 36 reports of familial multiple myeloma, described mostly in siblings, to which the authors add one more family. These patients did not differ significantly form those with non-familial myeloma with regard to sex, age, distribution of monoclonal proteins, clinical and laboratory data, and the course and prognosis of the disease. An increased incidence of immunoglobulin abnormalities was observed in healthy relatives of patients affected with familial myeloma. In most cases the time interval of the diagnosis of myeloma in a family member of a known patient was under 4 yr. These observations, in conjunction with reports of myeloma occurring in clusters in a community and the appearance of myeloma in spouses raise the possibility of an environmental factor (virus?) which may contribute to the pathogenesis of myeloma in genetically predisposed individuals. Multiple myeloma should be added to the list of neoplastic diseases in which the family history is relevant and in which genetic and possibly environmental factors may be pathogenetically involved. (Author abstract) (49 Refs)

19. MONOCLONAL GAMMOPATHIES IN THE ADULT POPULATION OF FINISTERE, FRANCE.

Saleun JP, Vicariot M, Deroff P, Morin JF
Centre Departemental de Transfusion Sanguine, 46 Rue Felix le Dautec, B.P. 454, 29275 Brest Cedex, France
J Clin Pathol; 35(1):63-68 1982

Three hundred and thirty-four monoclonal gammopathies were detected in the sera of 30,279 adults from Finistere. Monoclonal gammopathies (MG) are more common in Finistere than in Paris and their distribution is not homogeneous. IgG paraproteins are particularly common in the northeast of Finistere whereas IgM paraproteins are more common in the southwest. Family studies and the high degree of inbreeding would support the hypothesis that there is a genetic predisposition to develop MG but the occurrence of paraproteins among three non-consanguineous couples seems to favor the existence of an environmental factor. (Author abstract) (32 Refs)

SELECTED PRE-CLINICAL STUDIES

20. A SIMPLE METHOD FOR SODIUM DODECYL-SULFATE-POLYACRYLAMIDE GEL ELECTROPHORESIS ANALYSIS OF MONOCLONAL COMPONENTS.

Santoro C, De Marchi M, Carbonara AO
(c/o Carbonara) Istituto di Genetica Medica, Universita degli Studi di Torino, Via Santena 19, 10126 Torino, Italy
Ric Clin Lab; 11(4):337-342 1981

Monoclonal (M) components of various classes and subclasses of myeloma serum were separated by electrophoresis on cellulose acetate followed by elution and analysis by sodium dodecyl-sulfate-polyacrylamide gel electrophoresis. The procedure provided a simple method of analyzing a large number of samples using only very small amounts of each sample. Results allow improved characterization of molecular variants not detectable with immunochemical methods. (9 Refs)

21. VARIANTS OF AN INTERSPECIES HYBRIDOMA WITH ALTERED TUMORIGENICITY AND PROTECTIVE ABILITY AGAINST MOUSE MYELOMA TUMORS.

Baumal R, Musclow E, Farkas-Himsley H, Marks A
Dept. Pathology, Hosp. Sick Children, Univ. Toronto, Toronto, Ontario M5G 1X8, Canada
Cancer Res; 42(5):1904-1908 1982

Recent isolates of RX54-3 hybridoma cells (new cells) protect BALB/c mice against subsequent challenge with the tumorigenic myeloma parent cells used to construct this hybridoma. In contrast, hybridoma cells which have been maintained in tissue culture for long periods of time (old cells) are not protective. In the present study, we compared a number of properties of the new and old hybridoma c ells and determined which line was more similar to the parent myeloma. We found that new hybridoma cells resembled myeloma cells in: (a) possessing A- and C-type viral particles on transmission electron microscopy and a relatively smooth surface on scanning electron microscopy; (b) being sensitive to a hypotonic solution containing the dye propidium iodide; (c) having similar DNA histograms on flow cytometric analysis; (d) being sensitive to the bacteriocin colicin HSC10; and (e) being tumorigenic in nude mice. In contrast, old hybridoma cells differed in all of these characteristics from new hybridoma and myeloma cells. Therefore, in order to protect against challenge with the tumorigenic myeloma parent, hybridoma cells must retain properties of that parent. (Author abstract) (10 Refs)

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ICRDB CANCERGRAM

CLINICAL EVALUATION AND TREATMENT OF MULTIPLE MYELOMA AND OTHER GAMMOPATHIES

SERIES CT13 No. 82/09

SEPTEMBER, 1982

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PDQ (PROTOCOL DATA QUERY) - A NEW ONLINE CANCER DATABASE WILL BE AVAILABLE THIS FALL! PDQ LISTS THERAPY PROTOCOLS PLUS ADDRESSES AND PHONE NUMBERS OF CLINICAL INVESTIGATORS. CONTACT ICRDB FOR DETAILS.

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DIAGNOSIS

1. RADIOGRAPHY AND BONE SCINTIGRAPHY IN MULTIPLE MYELOMA: A COMPARATIVE ANALYSIS.

Ludwig H, Kumpan W, Sinzinger H
Div. Diagnostic Radiology, Univ. Vienna, Vienna, Austria
Br J Radiol; 55(651):173-181 1982

The sensitivity of radionuclide imaging for detecting skeletal lesions was compared with that of radiography by evaluating 573 different anatomical sites in 41 patients with multiple myeloma. Radiography revealed a significantly greater number of myeloma-related bone lesions than did radionuclide imaging. Of the 179 myeloma-related bone lesions detected when both techniques were applied, 163 were seen by radiography and 82 by radionuclide imaging. Ninety-seven lesions were detected by radiography alone and 16 lesions seen by scintiscanning only, yielding a sensitivity of 91% for the former and and of

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46% for the latter technique. Radionuclide imaging proved superior to radiography only occasionally in the rib cage, and rarely in other anatomical sites. These findings suggest that radiography is the method of first choice in obtaining a skeletal survey in patients with multiple myeloma. In cases with continued pain, unexplained by standard radiography, the skeletal survey should be supplemented by tomography and radionuclide imaging. (Author abstract) (15 Refs)

2. SERUM BETA-2-MICROGLOBULIN IN MULTIPLE MYELOMA: RELATION TO PRESENTING FEATURES AND CLINICAL STATUS.

Bataille R, Magub M, Grenier J, Donnadio D, Sany J
Service de consultation de Rhumatologie Sociale, Centre Gui-de-Chauliac, Hopital Saint-Eloi, 34059 Montpellier Cedex, France
Eur J Cancer Clin Oncol; 18(1):59-66 1982

Serum beta-2-microglobulin (B2m) levels were measured in 78 patients with multiple myeloma (MM) and were compared with values for normal individuals and patients with benign monoclonal gammopathies (BMG). Serum B2m levels and values corrected for renal function were significantly higher in patients with MM at time of diagnosis than in normal individuals (p less than 0.001) and were highly correlated with the total body burden of myeloma cells as derived from the staging system of Durie and Salmon. However there were no significant differences between values for BMG and low-mass MM. For patients evaluated following induction chemotherapy, there was also a clear correlation between serum B2m levels and the magnitude of tumor regression or progression (p less than 0.05). During the plateau-phase, serum B2m levels remained very stable and highly correlated with the residual tumor mass (p less than 0.001). It was concluded that (1) B2m was not a reliable marker to distinguish between BMG and low-mass MM and (2) B2m was a valuable marker for assessing initial tumor mass of patients with MM and response to chemotherapy (especially the plateau-phase), above all in patients with urine or low-serum monoclonal component levels (Author abstract) (33 Refs)

3. MULTIPLE MYELOMA AND RELATED CONDITIONS: AN IMMUNOPEROXIDASE STUDY OF PARAFFIN-EMBEDDED BONE MARROW BIOPSIES.

Martelli MF, Falini B, Tabilio A, Firenze A, Tribalto M, Aversa F, Grignani F, Mandelli F
Instituto di Clinica Medica Generale e Terapia Medica, Universita di Perugia, 06100 Perugia, Italy
Haematologica (Pavia); 67(1):1-16 1982

The peroxidase-antiperoxidase (PAP) technique was used to detect immunoglobulin heavy and light chains in sections of paraffin-embedded bone marrow biopsy material from 49 patients with multiple myeloma, 11 with Waldenstrom's disease, and 15 with benign monoclonal gammopathies. The findings were compared with those from a two-stage immunoenzymatic procedure (labeled antigen) in 10 of the IgG multiple myeloma patients. The PAP method allowed easy immunohistological typing, and in all but three cases the chain type corresponded with that seen in the serum or urine. In the three cases (light chain disease, anaplastic myeloma, and non-secretory myeloma), a light or heavy chain was detected that was not seen in the serum. The labeled antigen method was less sensitive but more specific than the PAP technique, and eliminated the background staining seen with the PAP method. Monoclonal immunoglobulin was detected within plasma cells in Waldenstrom's disease, but not on or in intermediate cells or small lymphocytes. Both anti-kappa and anti-lambda plasma cells were seen in the benign monoclonal gammopathies, with the ratio usually less altered than in the malignant gammopathies. The value of the PAP technique in immunohistological cell typing is discussed. (47 Refs)

4. CYTOCHEMICAL STUDIES OF BONE MARROW PLASMA CELLS IN MONOCLONAL GAMMOPATHIES.

Miliani A, Anichini P, Di Guglielmo R, Pellegrini G, Firorelli C, Cuccuini A, Cozzolino F, Verceli D
Istituto de Clinica Medical Generale, Universits di Firenze, Viale Pieracini 18, I-50139 Firenze, Italy
Nouv Rev Fr Hematol; 24(1):27-33 1982

Plasma cell ATPase, acid phosphatase (AP), and alpha-naphthyl acetate esterase (alpha-NAE) were studied in 166 bone marrow biopsies from 152 patients with myeloma (MM: 55 cases), benign monoclonal gammopathy [GMB: 33: 24 apparently idiopathic (GMBi), 9 secondary (GMBs)] polyclonal hypergammaglobulinemia (HP: 34), Waldenstrom macroglobulinemia (W: 4), and disorders other than gammopathies (T: 40). Mean scores of ATPase activity were reported for MM (23.23), GMBi (43.20), GMBs (29.43), HP (50.76), W (51.37) and T (52.22) subjects. Mean PA scores were 212.35 for MM patients, 188.21 for GMBi, 191.86 for GMBs, 184.57 for HP, 172.13 for T, and 184 for W. Mean alpha-NAE scores were 190.52 for MM patients, 158.73 for GMBi, 150.67 for GMBs, 146.37 for HP, 136.05 T, and 103.67 for W. ATPase scores were of diagnostic value in 42/44 biopsies from MM patients; PA and alpha-NAE results were more variable and less significant (14/23 and 17/27 biopsies, respectively). In examining MM and GMB patients, PA results showed the largest differences between GMB and MM. Better agreement with pathologicaly findings was obtained for tests indicative of MM than those for GMB. Low levels of ATPase, observed in 6/7 MM biopsies, indicate a need for further study due to the possibility of MM. (17 Refs) (In FRE)

CLINICAL IMMUNOLOGY AND IMMUNOTHERAPY

5. ENHANCED T CELL SUPPRESSION IS DIRECTED TOWARD SENSITIVE CIRCULATING B CELLS IN MULTIPLE MYELOMA.

Perri RT, Oken MM, Kay NE
Dept. Medicine, Hematology Section (111E), Veterans Admin. Medical Center, 54th St. and 48th Ave. South, Minneapolis, MN, 55417
J Lab Clin Med; 99(4):512-519 1982

Multiple myeloma, a disorder typically accompanied by monoclonal immunoglobulin excess and hypogammaglobulinemia was evaluated to delineate the status of T cell regulation on malignant B cell proliferation. Intact T cells and T cell subsets previously noted by us to be suppressor (Tgamma) and helper (T non-gamma) were isolated from 10 controls and 10 myeloma patients. Various concentrations of control and patient T cell subsets were mixed with control and patient B cells and stimulated with PWM. T cell effect on B cell proliferation as measured by [3H]thymidine incorporation was then determined. Myeloma Tgamma cells were more effective than control Tgamma cells in suppressing control or myeloma B cell [3H]thymidine incorporation. Interestingly, myeloma B cells, when added to myeloma Tgamma cells, were suppressed to a greater extent than were control B cells when

mixed with a similar concentration of myeloma Tgamma cells. These in vitro studies suggest a complexity of B and T cell abnormalities in multiple myeloma; first, the myeloma B cells are extremely sensitive to Tgamma cell suppression, and second, myeloma Tgamma cells have excessive suppressor capacity. It is yet unclear whether these results are associated with an immunoregulatory response to this malignancy or represent part of the basic disease process. (Author abstract) (22 Refs)

6. GASTRIC PLASMACYTOMA. AN IMMUNOLOGIC AND IMMUNOHISTOCHEMICAL STUDY.

Nakanishi I, Kajikawa K, Migita S, Mai M, Akimoto R, Mura T
Dept. Pathology, Sch. Medicine, Kanazawa Univ., 13-1, Takara-machi, Kanazawa, Ishikawa, 920, Japan
Cancer; 49(10):2025-2028 1982

A case of IgG (gamma) secreting plasmacytoma arising in the stomach has been presented. Immunohistochemically, the tumor cells contained IgG-lambda immunoglobulin. Immunoelectrophoretic study on patient's serum revealed in the gamma zone the presence of M protein which reacted specifically with anti-IgG and anti-lambda antisera. Agar electrophoresis and immunofixation electrophoresis with anti-IgG and anti-lambda antisera showed multiple subbands. Neuraminidase treatment of the purified IgG from this patient resulted in gradual reduction of four subbands to two. Electrophoretic charge difference of the monoclonal immunoglobulin may be attributed to incompletely synthesized sugar chains attached to the protein core. (Author abstract) (19 Refs)

CHEMOTHERAPY

7. CLINICAL STUDIES ON CHEMOTHERAPY FOR MULTIPLE MYELOMA. PART II: RESPONSE RATES, PROGNOSTIC FACTORS, AND SIDE EFFECTS IN MULTIPLE MYELOMA TREATED WITH MIP (PREDNISOLONE AND SEQUENTIAL MELPHALAN AND IFOSFAMIDE).

Adachi T
Second Dept. Internal Medicine, Okayama Univ. Medical Sch., Okayama, Japan
Okayama Igakkai Zasshi; 93(5/6):519-536 1981

This report consists of an analysis of 47 patients with multiple myeloma registered between October, 1975, and December, 1980. All of them received Prednisolone together with sequential Melphalan and Ifosfamide (MIP). Clinical studies of the response rates and prognostic factors were conducted and side effects and complications in the treatment of MIP were discussed. The results are summarized. MIP therapy seemed to be better overall in comparison to M, MP, and I. The 50% survival time in 47 patients treated with MIP followed from the initiation of treatment was 19 mo. In MIP therapy, the response rate was paradoxically higher in all clinical parameters in the advanced stage group than in the early and intermittent stages. This study made clear the relationship between the survival time and patients characteristics. Of clinical parameters, (1) age, (2) Stage IV in the clinical staging of Durie and Salmon, (3) hypercalcemia, (4) extensive bone lytic lesions and (5) Type IV in the pathomorphological stage of Brucher correlated with progressive life span shortage. Patients who responded rapidly had a longer duration of remission and longer survival than those who responded slow. In Stage III, patients who received MIP had a higher response rate and longer survival than those who received M + MP. Side effects and complications reported during MIP treatment were as follows: Bone marrow suppression, liver damage, respiratory infection, urinary infection, herpes zoster and lung fibrosis. (39 Refs) (In JPN)

CASE REPORTS

8. SOLITARY INTRACRANIAL PLASMACYTOMA.

Kohli CM, Kawazu T
550 Parmalee Ave., Youngstown, OH, 44510
Surg Neurol; 17(4):307-312 1982

A case of solitary plasmacytoma involving the left cerebral convexity, dura mater, falx, and sagittal sinus is reported. After undergoing subtotal excision, followed by radiation, the patient was still doing well 7 yr after diagnosis. The importance of electrophoretic studies of the cerebrospinal fluid protein and the serum protein is discussed. The literature on solitary intracranial plasmacytoma is reviewed. (Author abstract) (25 Refs)

9. PLASMA CELL MYELOMA SIMULATING KRUKENBERG'S TUMOR.

Bambirra EA, Miranda D, Magalhaes GM
Rua Turmalina 274 Prado, 30000 Belo Horizonte, MG, Brazil
South Med J; 75(4):511-512 1982

Pathologic diagnosis of plasma cell myeloma of the ovaries was confirmed by skeletal survey and bone marrow examination in a 44-yr-old woman who had presented with abdominal pain, nausea, and vomiting and had originally been diagnosed as having Krukenberg's tumor. Urinalysis was positive for Bence-Jones protein, and serum electrophoresis showed a homogeneous band migration through the gamma globulin region compatible with myeloma protein. Immunoelectrophoresis demonstrated an IgG type of myeloma. (2 Refs)

10. AMYLOIDOSIS MASQUERADING AS INFLAMMATORY BOWEL DISEASE WITH A MASS LESION SIMULATING A MALIGNANCY.

Johnson DH, Guthrie TH, Tedesco FJ, Griffin JW, Anthony HF
Div. Oncology, Dept. Medicine, Vanderbilt Univ., Nashville, TN, 37232
Am J Gastroenterol; 77(3):141-145 1982

Our patient, who was known to have multiple myeloma, presented with wt loss, rectal bleeding, and a barium enema study suggestive of a colitis with a mass lesion. Colonoscopy with biopsy revealed the mass to be large mucosal folds infiltrated with amyloidosis. Amyloidosis has been reported to mimic malignancy, mainly by tumorous deposits in the stomach and less commonly in the small and large bowels. Gastrointestinal surgery in patients with amyloidosis potentially may have undesirable consequences due to failure of anastomotic suture lines and subsequent sepsis. The knowledge that amyloidosis may be associated with multiple myeloma and an appreciation of the wide range of gastrointestinal roentgenographic findings in patients with amyloidosis should prompt the clinician to obtain endoscopic and biopsy evaluation of these patients. (Author abstract) (27 Refs)

SELECTED REPORTS ON ETIOLOGY AND EPIDEMIOLOGY

11. EPIDEMIOLOGIC AND AGE-DEPENDENT DATA ON MULTIPLE MYELOMA IN AUSTRIA.

Ludwig H, Fritz E, Friedl HP
Dept. Medicine II, Univ. Vienna, Vienna, Austria
JNCI; 68(5):729-733 1982

The mortality rates for multiple myeloma showed an increasing trend between 1969 and 1979, when multiple myeloma accounted for 6% of the reported cancer deaths in Austria. The median age of diagnosis was relatively high: 68.5 years for males and 69.0 years for females. The age-corrected male:female ratio of 1.23:1 indicated a higher incidence of multiple myeloma in males. Age-standardized (standard population for Europe) incidence rates amounted to 1.5/100,000 male inhabitants and 1.2/100,000 female inhabitants/year. In a subsample of patients with multiple myeloma, the paraprotein types as well as the kappa:lambda ratio resembled the frequency distribution of normal immunoglobulins. There were no age-related differences for the stages of the disease and the poor risk factors at diagnosis for patients 65 years old or younger or for those over 65 years of age at diagnosis. Survival rates were significantly higher for younger patients than for older ones, with a 50% survival time of 45 and 26 months, respectively. The differences resulted solely from the dissimilar general life expectancies in both groups, and survival rates with strict regard to multiple myeloma proved to be identical in younger and older patients. (Author abstract) (22 Refs)

12. SECOND MALIGNANCIES ASSOCIATED WITH CHEMOTHERAPEUTIC AGENTS.

Kyle RA
Mayo Clinic, Rochester, MN, 55905
Semin Oncol; 9(1):131-142 1982

Major aspects of second malignancies associated with chemotherapy are reviewed. Acute leukemia may result from chemotherapy for treatment of multiple myeloma; reported incidence of acute leukemia has varied from 0.2-7% and the reported actuarial rates at 4 to 5 yr have ranged from 4.8-19.6%. The most common chemotherapeutic agent implicated has been melphalan, po or iv, but cyclophosphamide and carmustine have also been associated with second malignancy. Acute myelocytic or myelomonocytic leukemia are most common, but erythroleukemia and acute lymphocytic leukemia have also been described. Other diseases for which chemotherapy has been associated with acute leukemia are discussed, including Waldenstrom's macroglobulinemia, Hodgkin's disease, non-Hodgkin's lymphoma, chronic lymphocytic leukemia, carcinoma of the breast, carcinoma of the ovary, other solid tumors, and nonneoplastic diseases. Care must be exercised in weighing the benefits of chemotherapy against possible second malignancy; the only valid test is long-term assessment of improved survival. Use of alkylating agents for nonmalignant diseases, such as rheumatoid arthritis, systemic lupus erythematosus, nephropathies, and dermatologic diseases does not seem warranted considering the risk of second malignancy. (87 Refs)

SELECTED PRE-CLINICAL STUDIES

13. SELECTION OF MYELOMA LINES SUITABLE FOR HYBRIDOMA.

Franssen JD, Herion P, Urbain J
Lab. Biological Chemistry, Univ. Brussels, rue de Chevaux, 67, Rhode-St.-Genese, Belgium
Protides Biol Fluid Proc Colloq; 29:645-648 1982

The large variation in the number of successful hybridomas in cell fusion experiments may be due in part to the loss of tumoral characteristics by the myeloma cell partner involved. To overcome this problem, more suitable myeloma cells may be selected on the basis of their growth potential in vivo and in soft agar. Myeloma cell subclones of S2/0-Ag 14 were selected on the basis of these criteria and cell fusion results. The subclones grow fast in vitro, and in vivo give high and reproducible rates of fusion: one hybrid per 10(4) input spleen cells. The recovered hybridomas display the inherited myeloma tumoral characteristics. (6 Refs)

14. HUMAN PLASMACYTOMA WITH AN UNUSUAL KARYOTYPE GROWING IN VITRO AND PRODUCING LIGHT-CHAIN IMMUNOGLOBULIN.

Karpas A, Fischer P, Swirsky D
Dept. Haematological Medicine, Cambridge Univ. Clinical Sch., Cambridge, England
Lancet; 1(8278):931-933 1982

A new human plasmacytoma line (Karpas 707) was established from the cells of the bone-marrow and peripheral blood of a patient with Bence-Jones-positive multiple myeloma. The cells of this new line resembled the patient's malignant cells and fresh myeloma cells from nine other patients in being Epstein-Barr viral nuclear antigen negative. They looked like plasma cells and they secreted only lambda light chains. Both these cells and the patient's fresh cells were hypodiploid and contained the Philadelphia chromosome and several other markers. This line seems to be the first human plasmacytoma line since the IgE lambda-producing line (U266) established in 1968, and it may be suitable for the production of human monoclonal antibodies. (Author abstract) (14 Refs)

15. A HUMAN PLASMA CELL LINE: INDUCTION AND CHARACTERIZATION.

Miller CH, Carbonell A, Peng R, Paglieroni T, MacKenzie MR
Dept. Pathology, Sch. Medicine, Univ. California, MS-1, Room 3453, Davis, CA, 95616
Cancer; 49(10):2091-2096 1982

A stable line of IgG K producing human plasma cells was established from a myelomatous human bone marrow using conditioned media from a rapidly metabolizing lymphoblast line, RPMI 4098. Growth in RPMI 1640 (15% fetal calf serum) at 6% CO2 promoted a 62-hr doubling time with a preferred cell concentration of 1 x 10(6)/mL. Surface marker studies showed: no receptors for sheep erythrocytes, no surface immunoglobulins, variable number of cells bearing complement receptors and 83% bearing Fc receptors. Although transmission electron micrographs demonstrated a poorly developed endoplasmic reticulum, radioimmunoassay showed 23 ng IgG and 28.7 ng Kappa were produced by 1 x 10(6) cells in 72 hr. Further, the cells are lipase, esterase and Epstein-Barr nuclear antigen negative. ASG banding showed a total chromosome number that varied from 46-49. Since the number of human plasma cell lines is limited, it is felt that this line will augment

the immunobiological study of human myeloma. (Author abstract) (16 Refs)

16. CHARACTERIZATION OF A MONOCLONAL ANTIBODY REACTIVE WITH A SUBSET OF HUMAN BREAST TUMORS.

Yuan D, Hendler FJ, Vitetta ES
(c/o Hendler) Dept. Internal Medicine, Univ. Texas Health Science Center at Dallas, 5323 Harry Hines Blvd., Dallas, TX, 75235
JNCI; 68(5):719-728 1982

Fusion of spleen cells, from mice immunized against the human hormone-dependent breast cancer cell line ZR-75-1, with murine myeloma cells resulted in the establishment of a hybridoma cell line, HY59-H10(H59). The purified monoclonal IgM produced by the hybridoma reacts with the most differentiated human breast tumor cell lines but not with cells derived from normal breast secretions or with numerous other malignant cell lines. Of 106 biopsy specimens examined, H59 bound to 54% of malignant breast specimens, to 83% of fibroadenomas, and to 82% of specimens containing fibrocystic disease. Binding could not be detected in uninvolved breast tissue. (Author abstract) (52 Refs)

17. A MONOCLONAL ANTIBODY DEFINING A BURKITT LYMPHOMA ASSOCIATED ANTIGEN.

Wiels J, Fellous M, Lenoir G, Tursz T
Laboratoire de Immunologie, Clinique Institut G. Roussy, 94800 Villejuif, France
Protides Biol Fluid Proc Colloq; 29:899-902 1982

Reactivity of monoclonal antibody 38-13, obtained by fusing murine myeloma cells with Lewis rat splenocytes sensitized with Daudi cells (human Burkitt lymphoma), was investigated. Negative results were obtained in all patients with B chronic lymphoid leukemia, acute lymphoid leukemia (T and nonT-nonB), acute myeloid leukemia, acute monoblastic leukemia, Hodgkin's disease, T cell lymphosarcoma, and B cell lymphosarcoma (nodular and diffuse). Positive results were obscrved in 4/8 patients with B cell Burkitt lymphoma. When the specific reactivity of 38.13 ascites was tested with a panel of cell lines of various origins, both by complement dependent lymphocytotoxicity tests and indirect membrane immunofluorescence assays, all the positive target cells were of Burkitt's lymphoma origin. Negative results were obtained with 15 Epstein-Barr virus positive lymphoblastoid cell lines, 4 T cell lines, a chronic myelogenous leukemia cell line, 4 teratoma cell lines, and one each of melanoma and neuroblastoma. The 38.13 monoclonal antibody may be useful for diagnosis and specific immunotherapy of Burkitt lymphomas. (8 Refs)

18. PREPARATION AND CHARACTERIZATION OF MONOCLONAL ANTIBODIES AGAINST ANTIGENS OF HUMAN RENAL ADENOCARCINOMA.

Hess H, Albeid U, Biermann S, Waks T, Scherberich JE, Mondorf AW, Schoeppe W, Senge T, Falkenberg FW
Dept. Nephrology, Center for Internal Medicine, Klinikum J. W. Goethe Universitat, 6000 Frankfurt am Main, W. Germany
Protides Biol Fluid Proc Colloq; 29:903-905 1982

Lymphocytes from BALB/c mice hyperimmunized by four and eight consecutive injections of renal adenocarcinoma plasma membranes were fused with X63-Ag 8.653 plasmacytoma cells. In the supernatants of 90/600 wells with viable cells, antibodies reactive with antigens in tumor and/or kidney were found. Twenty-two clones were isolated and characterized. Tumor cell membranes, capillaries and intercellular matrix were recognized by the various monoclonal antibodies. Generally, the density of antigenic determinants was higher in the tumor than in normal kidney tissue. No monoclonal antibodies were found that reacted exclusively with tumor. Localization of antigenic determinants in the kidney was easy, while in the tumor tissue localization could not be defined exactly. Antibodies of Hyp I 164 D5 and Hyp I 289 A1 reacted with tumor cell membranes, antibody Hyp I 238 A9 with capillaries. (5 Refs)

19. MONOCLONAL ANTIBODIES AGAINST CARCINOEMBRYONIC ANTIGEN.

Hedin A, Hammarstrom S
Dept. Immunology, Univ. Stockholm, Stockholm, Sweden
Protides Biol Fluid Proc Colloq; 29:907-910 1982

Monoclonal antibodies against carcinoembryonic antigen (CEA) were produced using a hybridoma technique. Spleen cells from BALB/c mice immunized with highly purified CEA were fused with mouse myeloma cell line Sp2/0-Ag 14. Data on eight monoclonal antibodies against CEA obtained from cells cultured for 4 mo are reported. All eight antibodies were IgG 1 and six showed different isoelectric points. Three different titration curves of supernatant reactivity were seen. Six of the eight antibodies were directed against conformation dependent epitopes on the CEA molecule since they showed a marked decrease in reactivity against reduced and alkylated CEA as compared to the native molecule. All antibodies showed approx equal reactivity against Smith degraded CEA compared to native CEA. It was concluded that the antibodies were directed against the protein moiety of the molecule. One antibody gave a precipitate when tested in immunodiffusion against CEA; however, when two different antibodies were combined and tested against CEA, strong precipitates were seen in several combinations. Thus, at least five antibodies recognize different epitopes on the CEA molecule. (6 Refs)

20. T LYMPHOCYTE-MEDIATED SUPPRESSION OF MYELOMA FUNCTION IN VITRO. IV. GENERATION OF EFFECTOR SUPPRESSOR CELLS SPECIFIC FOR MYELOMA IDIOTYPES.

Abbas AK, Takaoki M, Greene MI
Dept. Pathology, Harvard Medical Sch., Boston, MA, 02115
J Exp Med; 155(4):1216-1221 1982

BALB/c mice were injected iv with viable syngeneic splenocytes to which affinity-purified M315 IgA was coupled developed suppressor T cells (Ts1) that inhibited IgA plaque-forming cells (PFC) after greater than 2 days in culture. On the other hand, T cells induced by soluble extracts of Ts1 cells (TsF1) and sc immunization suppressed greater than 50% of the PFC within 1 day and 80-90% by day 4. The cells mediating rapid suppression were operationally termed effector Ts. The specificity of the effector Ts was assessed by their ability to bind to different myeloma proteins. Suppressive activity was depleted by absorbing effector Ts on dishes coated with M315 IgA but not on dishes coated with MPC11 (IgG2b,k of unknown specificity) or M460 proteins. M315-specific effector Ts did not inhibit MPC 11 cells and caused greater than 70% selective suppression of IgA secretion by the MOPC 315-MPC11 somatic cell hybrid. Effector Ts were Thy-1.2+, Lyt-1-2+ cells, while Ts1 were either Lyt-1+2+ or T lymphocytes bearing both Lyt-1+ and Lyt-2+ markers were necessary for Ts1 to induce or mature into effector Ts in vitro. The ability to induce two cell types at different stages of a suppressor pathway, and to measure their effects on a monoclonal, autono-

mous target, should facilitate analysis of the differentiation and mechanisms of action of suppressor T lymphocytes. (11 Refs)

21. HUMAN-MOUSE HYBRIDOMA CELLS PRODUCING ANTIBODIES.

Astaldi GC, Willems C, Alleyne W, Lansdorp P, Zeijlemaker WP, Janssen M
Central Lab., Netherlands Red Cross Blood Transfusion Service, Amsterdam, The Netherlands
Protides Biol Fluid Proc Colloq; 29:609-614 1982

Xenogeneic hybridomas between human lymphocytes and mouse myeloma cells were produced and the effects of various factors on their growth were studied. After fusion, cells were resuspended in culture medium containing 10% human endothelial culture supernatant (HECS) and when hybrid clones developed, the supernatants were tested for the presence of antibodies against RhD+ RBC. The hybridoma cells producing anti-D activity were expanded and cloned by limiting dilution in culture medium containing 10% HECS. Six days of culture in the presence of pokeweed mitogen strongly increased the yield of hybridoma cells. The recovery of hybridoma cells producing anti-D antibodies was significantly increased by culturing the lymphocytes in the presence of RhD+ RBC together with endothelial cells. All eight hybridoma supernatants agglutinating RhD+ RBC had specificity for the D antigen. Specific antibody production decreased markedly with time, indicating the instability of the xenogeneic hybridoma cells. Selection for antibody-producing clones was accomplished by culturing at low density and discarding negative clones. The percentage of wells containing hybridoma cells producing anti-D antibodies increased upon each passage up to the fourth passage, when a plateau was reached. Thus, when lymphocytes obtained from persons who had been immunized with allogeneic RhD+ RBC were fused with mouse myeloma cells, hybridoma cells were obtained producing specific anti-D antibodies. (13 Refs)

REVIEWS

22. PLASMA CELL NEOPLASMS.

Bergsagel DE, Rider WD
Dept. Medicine, Princess Margaret Hosp., Toronto, Ontario, Canada
Cancer - Principles and Practice of Oncology. DeVita VT, Hellman S, and Rosenberg SA, ed. Philadelphia, Lippincott, 1926 pp., 1982.

Plasma cell neoplasms are defined and discussed with respect to history, incidence, pathogenesis, anatomic considerations, pathology, diagnosis, staging, screening, differential diagnosis, treatment, special problems, survival and cause of death, and special syndromes. A spectrum of B-lymphocyte/plasma cell diseases, ranging from benign monoclonal gammopathy (BMG) to multiple myeloma (MM), is characterized by a homogeneous monoclonal protein (M-protein) in the serum and urine. BMG may progress to macroglobulinemia or a plasma cell tumor in about 30% of patients. Extramedullary plasmacytomas (75% involve the upper airways) can be prevented from progression by local radiotherapy (RT), provided that the tumor does not invade adjacent bone. Solitary plasmacytoma of bone seems to be an early stage of MM, with an exponential curve of progression to MM (median, about 5 yr) after successful local RT. In MM patients, the first goal of treatment is pain relief, which can be provided by local RT (if the deposits are osteolytic) or chemotherapy. Combination chemotherapy, can arrest the progression of MM for 1 to greater than 10 yr in most patients. Maintenance therapy does not improve the results. The lack of a correlation between tumor cell kill and the median survival time (MST) and the failure of more intensive chemotherapy to increase the MST suggest that the beneficial effects of treatment may not be caused by an effect of treatment on the tumor cell mass. Relapse is accompanied by pancytopenia (apparently unrelated to treatment), resistance to treatment, and rapid deterioration. The risk of leukemia increases exponentially in treated patients. However, the role of alkylating agents in the pathogenesis of leukemia is not clear. (319 Refs)

23. MONOCLONAL ANTIBODIES.

Milstein C
Medical Res. Council Lab. Molecular Biology, Cambridge, England
Cancer; 49(10):1953-1957 1982

Basic research on and clinical applications of monoclonal antibodies are discussed. Antibody structure, recognition and effector functions of antibodies, genetic control of antibodies, and advances in the study of antibodies and monoclonal antibodies through the examination of myelomas and related lymphoproliferative disorders are discussed. The monoclonal antibody produced by an isolated clone is a well-defined chemical which can be produced using nonpurified antigens. Production of monoclonal antibodies through fusion of an antibody-producing cell with a myeloma cell and creation of a permanent hybrid culture is described. A model is presented in which the immunogen is a tumor cell and one of the antigenic determinants is tumor specific. Potentially, monoclonal antibodies may be used as biological markers and therapeutic agents. (18 Refs)

U. S. GOVERNMENT PRINTING OFFICE: 1982—361-847/125

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CLINICAL EVALUATION AND TREATMENT OF MULTIPLE MYELOMA AND OTHER GAMMOPATHIES

SERIES CT13 No. 82/10

OCTOBER, 1982

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DIAGNOSIS

1. QUANTITATIVE CYTOLOGY IN MYELOMA RESEARCH.

Barlogie B, Latreille J, Alexanian R, Swartzendruber DE, Smallwood L, Maddox AM, Raber MN, Drewinko B

Dept. Developemental Therapeutics, M. D. Anderson Hosp. and Tumor Inst., 6723 Bertner Ave., Houston, TX, 77030

Clin Haematol; 11(1):19-46 1982

The role of quantitative cytology in myeloma research is discussed. Cytometric probes applicable to myeloma research include markers of neoplasia or tumor differentiation and cytokinetic descriptors. DNA content measurements may provide prognostically relevant information on intrinsic tumor cell properties such as ploidy and proliferative activity. Additional methods of characterizing the minor proportion of diploid plasma cells include analysis of RNA, overall protein, cytoplasmic Ig, and nucleolar antigen content. Cytokinetic marker techniques include DNA specific probes, DNA denaturation, and quenching of DNA probes. (58 Refs)

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2. MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE (MGUS): A REVIEW.

Kyle RA
Dept. Medicine, Mayo Medical Sch., Rochester, MN, [illegible]01
Clin Haematol; 11(1):123-150 1982

Findings in 241 patients with monoclonal gammopathy of undetermined significance (MGUS) are reported. At 5 yr follow up no significant increase of monoclonal serum protein (MP) or urine protein (UP) was found in 57% of cases. Death before the 5 yr study occurred in 23% of cases. Findings at 10 yr follow up included no significant increase of MP or UP in 38% of cases and death without 'myeloma, etc' in 35% of cases. Differentiating characteristics of MGUS include normal Hb and serum albumin concentrations, less than 2.0 g/deciliter MP in serum, no MP in urine, less than 5% plasma cells in bone marrow, and no osteolytic lesions. (93 Refs)

3. VALUE OF THE ESTIMATION OF BETA-2-MICROGLOBULIN IN THE SURVEILLANCE OF MYELOMAS. 290 ESTIMATIONS.

Kaltwasser P, Sauger F, Le Loet X, Pasquis P, Monconduit M, Deshayes P
Service de Rhumatologie, CHR La Prevotiere, F76230 Boisguillaume, France
Rev Rhum Mal Osteoartic; 49(5):359-363 1982

The correlation between beta-2-microglobulin (B2M) and serum creatinine was determined. The ratio of measured B2M and theoretical B2M as a marker for the progression of multiple myeloma was compared with that of the more common markers (immunoglobulin measurements and calculation of tumor mass) of the disease. Measurement of the B2M ratio correlated well with the calculations of tumor mass and immunoglobulin for the 290 sera examined. (32 Refs) (In FRE)

CLINICAL IMMUNOLOGY AND IMMUNOTHERAPY

4. INTERFERON TREATMENT FOR MULTIPLE MYELOMA.

Alexanian R, Gutterman J, Levy H
Dept. Medicine, M. D. Anderson Hosp. and Tumor Inst., 6723 Bertner Ave., Houston, TX, 77030
Clin Haematol; 11(1):211-220 1982

Clinical utility of interferon and of a potential interferon stimulator in 21 patients with multiple myeloma is discussed. Clinical trials with interferon in previously untreated patients showed a response in 3/12 cases (50% tumor mass reduction), some effect in 2/12 cases, and no effect in 7/12 cases. Remission duration ranged from 4-33 mo. Infusion of a derivative of a complex of polyriboinosinic and polyribocytidylic acids led to marked elevations of serum interferon in 18/20 patients with myeloma or lymphoma; no objective benefit was observed. (18 Refs)

5. T LYMPHOCYTE SUBSETS IN MULTIPLE MYELOMA (MM) PATIENTS (PTS) WITH ACTIVE AND STABLE DISEASE (MEETING ABSTRACT)

Ludwig CU, Hicks MJ, Durie BG, Tabing T
Cancer Center, University of Arizona Health Sciences Center, Tucson, AZ, 85724
Proc Am Soc Clin Oncol; 1:C-744 1982

Thirty-one MM pts and 31 healthy adults had measurements of total peripheral blood T-lymphocytes (OKT3), the helper/inducer subset (OKT4), the suppressor/cytotoxicity subset (OKT8) and the OKT4/OKT8 ratio. Controls (16 males [m] and 15 females [f]) had similar numbers of total T-cells and suppressor cells (%). However, f showed a significantly higher relative number of helper cells (OKT4) compared to men. MM pts were divided in two groups depending on the activity of the disease: 6 m and 8 f pts with stable disease, 13 m and 4 f with active disease. In pts with stable disease a significant increase in OKT8 combined with a significant decrease in OKT4 was seen resulting in a dramatic reduction in the OKT4/OKT8 ratio compared to the controls. In pts with active disease some reduction of the OKT3 was noted, but no significant change in the OKT4/OKT8 ratio. Since the change in the OKT4/OKT8 ratio with stable disease occurred in pts both on and off treatment, it would seem to reflect a characteristic of the stable disease state. This was further emphasized by the significant difference in OKT4/OKT8 ratio between stable pts and pts with active disease on treatment. It is therefore concluded that the relative increase of the suppressor cells (OKT8) in pts with stable disease may reflect a mechanism of disease control in MM. (no Refs)

6. EMERGENCE OF B-IMMUNOBLASTIC SARCOMA IN PATIENTS WITH MULTIPLE MYELOMA: A CLINICOPATHOLOGIC STUDY OF 10 CASES.

Falini B, De Solas I, Levine AM, Parker JW, Lukes RJ, Taylor CR (c/o Taylor) Dept. Pathology, Univ. Southern California, Los Angeles, CA, 90033
Blood; 59(5):923-933 1982

Immunologic and histologic studies were performed in 10 cases of myeloma that showed progression to a more aggressive proliferation, designated as immunoblastic sarcoma of B-cell type (B-IBS). Several patterns of clinical presentation were observed: eight patients showed typical multiple myeloma, four developed B-IBS within the bone marrow, and four developed B-IBS in multiple extramedullary sites; the remaining two patients had relatively localized myeloma, but also showed development of extramedullary B-IBS. The implications of these findings are discussed with regard to their prognostic import and their relationship to current concepts of plasma cell development. (Author abstract) (49 Refs)

CHEMOTHERAPY

7. PEPTICHEMIO INDUCTION THERAPY IN MYELOMATOSIS.

Merlini G, Gobbi PG, Riccardi A, Riva G, Sardi C, Perugini S
Inst. Medical Pathology I, Policlinico S. Matteo, Univ. Pavia, I-27100 Pavia, Italy
Cancer Chemother Pharmacol; 8(1):9-16 1982

Clinical results of peptichemio (PTC)-treatment obtained in 15 patients (8 males, 7 females; 30-74 yr old; 13 with multiple

myeloma, 2 with plasma cell leukemia), of whom 7 had been resistant to standard alkylating agents or prednisone (PD) therapy, are reported. PTC was administered iv at doses of 40-80 mg/48 hr in courses including 4-17 administrations, each in association with 'moderate' doses of PD (15-50 mg/day) and high doses of androstanes (testosterone enanthate or methenolone enanthate, 250 mg/wk). The PTC-treatment induced a rapid analgesic effect and improvement of general condition in all symptomatic patients. PTC significantly reduced the serum M-component (MC) in 13 patients; the median time of response was 32 days. The modifications of bone marrow plasma cell percentages were mainly in accordance with the changes of MC. PTC-treatment induced eight complete responses, five partial responses, and no response in two patients. The therapeutic results did not appear to be correlated with the PTC dosage. Treatment with low or medium doses of melphalan and cyclophosphamide after PTC prolonged remission for 5-31 mo in eight patients, inducing a further reduction of MC in two patients. Survival cannot be ascribed to PTC alone, since patients were treated with different drugs. The median survival time was 43+ mo from diagnosis and 16+ mo from the beginning of PTC therapy. The most serious non-hematologic side-effect was phlebothrombosis. Alopecia was observed in three patients. In 3/15 patients, leukocytes dropped below 1,500/cubic mm (mm3), and 6/15 patients had thrombocytopenia (less than 50,000 mm3) without bleeding. The cytopenic effect was rapidly reversible at suspension of treatment. (33 Refs)

8. COMBINATION CHEMOTHERAPY (M-2) PROTOCOL (BCNU, CYCLOPHOSPHAMIDE, VINCRISTINE, MELPHALAN, AND PREDNISONE) FOR WALDENSTROM'S MACROGLOBULINEMIA: PRELIMINARY REPORT.

Case DC
Div. Hematology and Oncology, Dept. Medicine, Maine Medical Center, Portland, ME, 14102
Blood; 59(5):934-937 1982

Fourteen consecutively referred, symptomatic patients with Waldenstrom's macroglobulinemia (ages 52-87 yr) have been treated with the five-drug M-2 protocol (carmustine (BCNU), cyclophosphamide, vincristine, melphalan, and prednisone). Three patients were previously treated and 11 patients were untreated. The majority of patients were symptomatic from hyperviscosity. All patients have responded to therapy. Two patients have achieved complete remissions and 12 patients partial remissions to date. None of the patients with symptomatic hyperviscosity has required plasmapheresis since therapy with the M-2 has been initiated. Lymphadenopathy, hepatosplenomegaly, and anemia have also responded to treatment. Follow-up data are limited, with survival from initiation of therapy with the M-2 ranging from 2+ to 35+ mo (median 17+ mo) (2+-40+ mo from time of diagnosis). Combination chemotherapy for Waldenstrom's macroglobulinemia with the M-2 protocol appears to increase the response rate in patients with symptomatic disease. Further survival analysis will be carried out. (Author abstract) (16 Refs)

9. RESPONSE AND SURVIVAL IN MULTIPLE MYELOMA WITH CTX, MEL, BCNU, VCR, PRED (M2 PROTOCOL) (MEETING ABSTRACT)

Paccagnella A, Salvagno L, Chiarion-Sileni V, Cartei G, Vinante O, De Besi P, Fosser V, Fornasiero A
National Cancer Institute, Bethesda, MD, 20205
Proc Am Soc Clin Oncol; 1:C-720 1982

From May 1975, 63 consecutive, untreated patients (pts) received the Lee M2 protocol (cyclophosphamide, melphalan, carmustine, vincristine, prednisone). In responding pts therapy was stopped after 10 mo. At relapse M2 was resumed until remission or death. Fifty-six pts had a long enough follow up to be evaluated for response and survival. Objective Response (OR) was defined a 50% reduction in paraprotein production rate; duration of response was calculated from this point; relapse was defined a 25% increase from the lower value attained. A total of 44/56 pts obtained OR, 32 of them had a OR greater than 75%. Maximum response was obtained on average at 5th cycle; median duration of response was of 21 mo; the overall Median Projected Survival (MPS) was of 51 mo. The 35 pts in III stage had a MPS of 46 mo, MPS of responders was 63 mo vs 8 mo of non responders. For MPS there is a trend in favor of pts with OR greater than 75% vs pts with OR 50-75%. Lee's data, both in response rate and survival, were confirmed in our case material where responders did not receive maintenance therapy but only reinduction on relapse. (1 Ref)

10. THE CONTRIBUTION OF PREDNISONE TO THE EFFECTIVENESS OF HEXAMETHYLMELAMINE (HXM) IN MULTIPLE MYELOMA (MM) (MEETING ABSTRACT)

Oken MM, Lenhard RE, Anderson J, Silverstein MN, Glick JH
University of Minnesota, Minneapolis, MN, 55417
Proc Am Soc Clin Oncol; 1:C-725 1982

From 3/78 to 12/81 ECOG evaluated HXM in 61 patients (pts) with heavily pretreated MM. Three regimens were utilized in sequential series of pts: Regimen A - HXM 200 mg/M2 day 1-21; Regimen B - HXM 280 mg/m2 day1-21 + pyridoxine (B6); Regimen C - HXM 280 mg/M2 day1-21 + B6 + prednisone 75 mg day1-7. Twenty-eight day treatment cycles were employed. Objective response (OR) required a greater than or equal to 50% decrease in serum M-protein or a 90% decrease in urinary light chain excretion. Objective improvement (I) required symptomatic improvement (SI), usually in the form of pain relief in addition to a 25-49% decrease in serum M-protein or a 50-90% decrease in urine light chain excretion. None of the 37 pts receiving regimens A or B had an OR compared with 25% of pts on regimen C, the only program with prednisone. The OR + I response rate of 50% on regimen C exceeded the 8% rate with regimen A and B. The 13 pts achieving OR or I had received a median of 2 prior chemotherapy regimens. It is unlikely that the 10 pts responding to regimen C responded to the prednisone alone since 9 of these pts had previous treatment failure on regimens containing prednisone in similar dose and schedule. Six had received 2 prior prednisone-containing regimens. (no Refs)

11. MULTIPLE MYELOMA: PROGNOSTIC INFLUENCE OF INITIAL M COMPONENT AND RESPONSE (MEETING ABSTRACT)

Lenhard RE, Woo KB, Humphrey RL
The Johns Hopkins Oncology Center, Baltimore, MD, 21205
Proc Am Soc Clin Oncol; 1:C-727 1982

Twenty-five patients with multiple myeloma who had poor prognosis or were resistant to conventional therapy were treatexd with cyclophosphamide given in IV bolus 60 mg/kg (2400 mg/M(2)). All patients had measurable serum M component (IgG, IgA). Early response to treatment was evaluated at 28 days and responses classified as objective (OR) greater than or equal to 50% decrease; improved (I) less than 50% decrease; and progression (PG), any increase in M component. Of the 25 patients, seventeen (68%) had decrease in M component (10/25 OR, 7/25 I) and 8 (32%) had PG at 28 days. Survival was ana-

lyzed relative to the pretreatment level of M component and to the response status at 28 days. Patients with OR and I had statistically higher median pre-treatment M component than those with PG: OR 7200 (mg/dl), I 4280, PG 2250. Median duration of survival has an inverse relationship to response at 28 days: OR 272 (days), I 382, PG 446, but these were not statistically different. This study suggests that among other factors, the pretreatment level of M component and the response status at 28 days appear to be of prognostic value. (no Refs)

RADIOTHERAPY

12. HEMI-BODY IRRADIATION IN MULTIPLE MYELOMA RELAPSING AFTER OR RESISTANT TO CHEMOTHERAPY (MEETING ABSTRACT)

Mill WB, Broun GO, Glasgow GP, Cohen HJ
Southeastern Cancer Study Group, Birmingham, AL, 35294
Proc Am Soc Clin Oncol; 1:C-743 1982

This study was designed to assess the efficacy and toxicity of hemi-body irradiation (HBI) in patients with advanced multiple myeloma no longer responding to first or second line chemotherapy. Nine patients were entered in the study. Four of the 9 received both upper hemi-body (UHB) and lower hemi-body (LHB) treatment in that sequence with a minimal interval of 6 weeks. The overall response with partial relief of pain was 61% (8/13). The duration of pain relief varied from 2 to 8 weeks with a median of 4 weeks. Toxicity was moderately severe as anticipated. Bone marrow toxicity was thought to have contributed to the death of 2 patients. Two patients developed mild gastrointestinal toxicity after UHB treatment. We have concluded from this pilot study that HBI as was given to these patients is effective in partially relieving pain, but only for a short period of time and this degree of palliation is not sufficient to warrant the toxicity. (no Refs)

MULTIMODAL THERAPY

13. TREATMENT OF MULTIPLE MYELOMA (MM) WITH CHEMORADIOTHERAPY AND IDENTICAL TWIN BONE MARROW TRANSPLANTATION (BMT) (MEETING ABSTRACT)

Fefer A, Greenberg PD, Cheever MA, Appelbaum FR, Bluming AZ, Storb R, Thomas ED
University of Washington, Seattle, WA, 98195
Proc Am Soc Clin Oncol; 1:C-731 1982

In 6/78 MM was diagnosed in a 49 y/o woman with back pain, marrow plasmacytosis and a serum gamma-globulin spike of 4.85 gm% containing a monoclonal IgG kappa. The patient received a total of 10 courses of melphalan (12 mg/d x 4d) and prednisone (60 mg/d x 4d) at 6 week intervals, and achieved a partial response, but was referred for BMT in 9/79 due to an increasing spike and worsening symptoms with severe back and rib pain. Evaluation on admission revealed compression fractures of T11-12, diffuse osteoporosis without lytic leisons, Hct 35, WBC 3360, platelets 354,000, marrow plasma-cytosis, albumin 3.6 gm%, IgG spike of 4.5 gm%, serum IgM of 18 mg% and IgA of 10 mg%. She received iv cyclophosphamide (60 mg/kg/d x 2), total body irradiation (200 rad daily x 6), and iv marrow infusion from her genetically identical twin on 9/28/79 (day 0). The absolute granulocyte count dropped to 0 but rose to greater than 500 by day 16. Platelet support was not required after day 12. The major clinical problem was immobilization secondary to pain from progressive compression fractures of T11-L5. Follow-up at 26 months (mos) after BMT revealed the patient to be fully functional with a normal CBC and bone marrow. The gamma globulin spike had decreased to 3.2, 1.5 and 1.1 gm% at 2, 12 and 24 mos, respectively. After 24 months, quantitative immunoglobulins revealed a normal IgM of 87 mg%, subnormal IgA of 55 mg%, and an IgG of 1388 mg% which contained the monoclonal protein. (no Refs)

CASE REPORTS

14. CASE REPORT: NON SYMPTOMATIC HYPERCALCEMIA IN A MYELOMA PATIENT.

Hazani A, Silvian I, Tatarsky I, Spira G
(c/o Spira) Dept. Hematology, Faculty Medicine, Technion-Israel Inst. Technology, P.O.B. 9649, Haifa, Israel
Am J Med Sci; 283(3):169-173 1982

An asymptomatic hypercalcemic IgG-Kappa myeloma patient is presented. A calcium-IgG complex was isolated and purified from the serum by column chromatography. Following further purification on a Sepharose protein A column, the IgG-Kappa molecule did not contain any detectable amount of calcium, indicating that calcium is lossely bound to IgG. The monoclonal IgG demonstrated a strong calcium binding capacity in vitro. The calcium-IgG complex in the serum was shown not to be saturated and thus could absorb more ionized calcium. In view of the presence of an abnormal monoclonal IgG capable of binding excess calcium, and the fact that the asymptomatic patient did not respond to the anti-hypercalcemic drugs, the treatment was stopped. (Author abstract) (9 Refs)

15. RETROPERITONEAL PLASMACYTOMA.

Rygaard A, Schonbeck P, Widding E, Frimodt-Moller C
(c/o Frimodt/Moller) Urologisk afdeling H, Kobenhavns amts sygehus i Gentofte, DK-2900 Hellerup, Denmark
Ugeskr Laeger; 144(13):952-953 1982

Large retroperitoneal mass surrounding the entire left kidney was demonstrated by ultrasonography in an 85-yr-old woman hospitalized for intermittent abdominal pains, loss of weight and changes in the defecation pattern. Fine-needle biopsy failed to reveal any tumor. The patient died without treatment. Autopsy revealed extramedullary plasmacytoma of the retroperitoneal space with close relation to the kidneys. The findings indicate that symptoms originating from the renal region do not necessarily indicate renal tumors, and that retroperitoneal tumors must be taken into consideration as well. (7 Refs) (In DAN)

16. BONE MARROW TRANSPLANTATION IN MULTIPLE MYELOMA: A CASE REPORT WITH PROTEIN STUDIES (MEETING ABSTRACT)

Higby DJ, Brass C, Fitzpatrick J, Henderson ES
Roswell Park Memorial Institute, Buffalo, NY, 14263
Proc Am Soc Clin Oncol; 1:C-747 1982

A 46-year-old patient with progressive multiple myeloma (IgGKappa type), who had relapsed after successful treatment with prednisone and L-PAM (L-phenylalanine mustard) and

again after treatment with cytoxan and prednisone, was treated with cytoxan 60 mg/kg daily for two days, followed by total body irradiation 800 R at 12 R per minute using a 4 Mev linear accelerator. A bone marrow transplant from an HL-A identical, MLC (mixed leukocyte culture) non-reactive sister was then given. Following a complicated course, the patient underwent a successful marrow engraftment with chimerism being identified. The patient's monoclonal paraprotein fell from 8.6 gm% to normal levels within three months, at a rate compatible with the known rate of IgG catabolism/excretion. During the ensuing six months since leaving the hospital, the patient has demonstrated a return of polyclonal IgG to normal levels, and in addition, had normal levels of both IgM and IgA, neither of which was present in detectable levels for five years preceding the transplant. (no Refs)

17. PLASMACYTOMA OF THE URETHRA.

Campbell CM, Smith JA, Middleton RG
(c/o Smith) 50 N. Medical Drive, Salt Lake City, UT, 84132
J Urol; 127(5):986 1982

Extramedullary plasmacytomas are rare tumors occurring most commonly in the upper respiratory tract. These tumors rarely have been reported in the genitourinary system. We report the first known case of a plasmacytoma of the urethra, in this instance a probable late metastasis. (Author abstract) (7 Refs)

SELECTED REPORTS ON ETIOLOGY AND EPIDEMIOLOGY

18. PLASMA CELL NEOPLASMS AND ACUTE LEUKAEMIA.

Bergsagel DE
Dept. Medicine, Princess Margaret Hosp., 500 Sherbourne St., Toronto M4X 1F9, Canada
Clin Haematol; 11(1):221-234 1982

The incidence of acute leukemia in patients with plasma cell neoplasms (PCN), clinical features, incidence of other tumors, and contributing factors are reviewed. The incidence of acute leukemia in myeloma patients has ranged from 29-230x the predicted incidence in normal individuals. The preleukemic phase in patients with PCN is characterized by pancytopenia and dyserythropoietic changes. The leukemic phase is characterized by plasma cells or plasmacytoid lymphocytes which produce the M protein, and leukemic cells in the bone marrow. Chromosome abnormalities have been noted frequently in patients with PCN and acute leukemia. (70 Refs)

SELECTED PRE-CLINICAL STUDIES

19. IN VITRO CLONING AND CHEMOSENSITIVITY OF HUMAN MYELOMA STEM CELLS.

Salmon SE
Section Hematology and Oncology, Univ. Arizona Coll. Medicine, Tucson, AZ, 85724
Clin Haematol; 11(1):47-63 1982

Biological and clinical observations of soft agar culturing and chemosensitivity of myeloma stem cells are reported. Maximal plating efficiency of tumor cells was 0.3%. Factors affecting cell growth included substitution of type O cells in the feeder layers with A, B, or AB RBC, conditioned media from BALB/c mice, and mercaptoethanol. The myeloma stem cell assay appears capable of predicting clinically meaningful drug sensitivity in myeloma with 79% accuracy and resistance with 95% accuracy. The most active drugs in myeloma include melphalan, carmustine, vinblastine, and adriamycin. (38 Refs)

20. IDIOTYPE-BEARING LYMPHOID CELLS IN PLASMA CELL NEOPLASIA.

Mellstedt H, Holm G, Pettersson D, Peest D
Dept. Radiobiology, Karolinska Hosp., S-10401 Stockholm, Sweden
Clin Haematol; 11(1):65-86 1982

Current evidence for the existence of B lymphocytes as part of the tumor cell clone in multiple myeloma (MM) is discussed and related to tumor cell differentiation and progression. B lymphocytes carrying the light chain isotype of the myeloma protein are selectively increased in the blood of approx half of untreated patients and are also found in the bone marrow when not detected in peripheral blood. Further evidence for the existence in MM of monoclonal B lymphocytes is provided by the varying expression of IgG-Fc- and C3-receptors on idiotypic cells; the presence of idiotypic Ig in some cell cytoplasm; and the morphology of lymphocytes, lymphoplasmacytoid cells, or plasma cells. (60 Refs)

21. ESTABLISHMENT AND CHARACTERIZATION OF A HUMAN MYELOMA CELL LINE (KMM-1).

Togawa A, Inoue N, Miyamoto K, Hyodo H, Namba M
Dept. Internal Medicine, Kawasaki Medical Sch., Kurashiki-shi, Japan
Int J Cancer; 29(5):495-500 1982

A new cell line (KMM-1) was established from a subcutaneous plasmacytoma of a 62-yr-old male with multiple myeloma. Immunological studies indicated that cultured cells were derived from the same clone of myeloma cells in vivo: smeared cells were stained with fluorescein-conjugated globulin of antisera monospecific to lambda-chain, and lambda-chains in the cell extracts and in culture media were identical to the Bence-Jones protein found in the patient's urine. The cell line grew in suspension with a doubling time of 36-40 hr and contained primitive plasmablastoid cells with prominent nucleoli and rough endoplasmic reticulum. Cells had the karyotype of 47, X, -Y, Iq+,-2, +t(1:2) (cen:cen), +7, 12q+, 14q+, +mar and carried no Epstein-Barr virus-determined nuclear antigen. Surface markers were as follows; E rosette (-), IgG Fc receptor (-), C3 receptor (-), S-Ig (+), TdT (-), asialo-GM1 (-). The reasons for the successful establishment of the myeloma cell line are discussed. (Author abstract) (23 Refs)

22. HUMAN MYELOMA CELL LINE CARRYING A PHILADELPHIA CHROMOSOME.

Karpas A, Fischer P, Swirsky D
Dept. Hematological Medicine, Cambridge Univ. Clinical Sch., Cambridge CB2 2QL, England
Science; 216(4549):997-999 1982

A new human plasmacytoma cell line (Karpas 707) has been established from a myeloma patient. The culture cells are negative for Epstein-Barr viral nuclear antigen and free of mycoplasma. They are similar to plasma cells and secrete only lambda light chains. The cells are hypodiploid and contain the Philadelphia chromosome and other abnormalities. This cell

line must be suitable for the production of human monoclonal antibodies. (Author abstract) (16 Refs)

REVIEWS

23. THE CURRENT STATUS AND FUTURE PROSPECTS OF TREATMENT FOR MULTIPLE MYELOMA.

Durie BG, Salmon SE

Dept. Internal Medicine, Univ. Arizona Health Sciences Center, Tucson, AZ, 85724

Clin Haematol; 11(1):181-210 1982

Details of therapeutic programs for multiple myeloma (MM) are reviewed. Median survival reported for patients receiving single or combination alkylating agent chemotherapy has ranged from 23 to 38 mo and 26 to 48 mo, respectively. Responses to chemotherapy include relief of bone pain, reversal of hypercalcemia, and gradual recovery of anemia. No significant difference in median remission duration is apparent between patients receiving various chemotherapeutic agents and no treatment. Complications in MM patients include hypercalcemia, neurologic problems, osteolytic bone destruction, anemia, infection, and renal failure. (90 Refs)

24. STAGING AND KINETICS OF MULTIPLE MYELOMA.

Durie BG

Dept. Internal Medicine, Univ. Arizone Health Sciences Center, Tucson, AZ, 85724

Clin Haematol; 11(1):3-18 1982

Staging and kinetics of tumor growth in multiple myeloma are discussed and related to prognosis and treatment decisions. Cases of multiple myeloma can be divided into three stages based on clinical parameters which correlate with measured cell mass. Staging and intrinsic drug sensitivity of the predominant myeloma cell clone are major determinants of response to treatment and survival. Tumor regression kinetics provide the basis for a rational approach to intensive initial induction therapy and to selection of the type and duration of maintenance therapy. (51 Refs)

25. IMMUNOREGULATORY CIRCUITS IN MYELOMA.

Ulrich S, Zolla-Pazner S

Dept. Pathology, New York Univ. Medical Center, 550 First Ave., New York, NY, 10016

Clin Haematol; 11(1):87-111 1982

Studies on the mechanisms by which malignant plasma cells depress host immune response in myeloma are reviewed. Ig secreted by plasma cells feeds back via the immune network, causing expansion and suppression of clones of cells that regulate the humoral response. Other plasma cell secretions mediating the immune response include osteoclast activating factor, interferon, and PC-factor. Plasma cell Ig secretion can be altered by T cells specific for myeloma idiotype, for antigens, or for receptors. (88 Refs)

26. LOCALIZED PLASMACYTOMAS.

Bataille R

Service de Consultation de Rheumatologie Sociale, Centre Gui de Chauliac, 34059 Montpellier Cedex, France

Clin Haematol; 11(1):113-122 1982

Clinical features, long term follow-up, prognosis, relation to multiple myeloma (MM), and management of solitary myelomas (SM) and of extramedullary plasmacytomas (EMP) are reviewed. SM is associated with skeletal pain relating to the tumor and affects a greater number of males than females; mean age of 114 patients with SM was 51 yr. Most patients with SM eventually develop MM. EMP commonly occurs in the upper respiratory tract and oral cavity. Diagnosis of SM or EMP can only be established histologically. Management techniques include biopsy, radiotherapy, surgery, and adjuvant chemotherapy in patients with evidence of subclinical dissemination. (28 Refs)

27. AMYLOIDOSIS.

Kyle RA

Dept. Medicine, Mayo Medical Sch., Rochester, MN, 55901

Clin Haematol; 11(1):151-180 1982

Pathogenesis, classification, involvement of organ systems, prognosis, and therapy for primary and secondary amyloidosis are described. Amyloidosis can be classified according to fibril content: mainly of light chains or of protein. Patients with primary amyloidosis can be distinguished from those with amyloidosis and multiple myeloma, based on the appearance and number of plasma cells in the bone marrow, the amount of monoclonal protein in the serum and urine, and the presence or absence of skeletal lesions. (190 Refs)

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ICRDB CANCERGRAM

CLINICAL EVALUATION AND TREATMENT OF MULTIPLE MYELOMA AND OTHER GAMMOPATHIES

SERIES CT13 No. 82/11 NOVEMBER, 1982

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DIAGNOSIS

1. LYMPHOGRAPHIC FINDINGS IN MULTIPLE MYELOMA.

Tallroth K, Somer K, Somer T
Dept. Radiology, Meilahti Hosp., Haartmaninkatu 4, 00290 Helsinki, Finland
Lymphology; 15(1):14-17 1982

The lymphographic appearances of the retroperitoneal lymph nodes in 10 patients with multiple myeloma have been analyzed. None of the patients had any signs of extramedullary involvement of myelomatosis before lymphography. In three cases irregular filling defects suggestive of myelomatous involvement were found. In one case they were close to a myelomatous bone lesion, whereas in the others the lymphographic abnormality was totally unexpected. In all three patients other nodes showed reactive hyperplasia. Such nonspecific hyperplasia was also encountered in three other cases. In two cases the myelomatous involvement of lymph node was detected before the diagnosis was recognized which is contrary to the belief that multiple myeloma involve nodes late in the disease. In addition to diagnostic aid the lymphographic demonstration of the myelomatous spread into lymph nodes may influence on the selection of the therapeutic approach to the disease. (Author abstract) (13 Refs)

2. GENETIC ASPECTS OF SUSCEPTIBILITY TO MULTIPLE MYELOMA.

Ludwig H, Mayr W
Dept. Medicine II, Univ. Vienna, Garnisongasse 13, A-1090 Vienna, Austria
Blood; 59(6):1286-1291 1982

An up-dated survey of the information pertaining to the role of genetic factors in susceptibility to multiple myeloma is attempted. Our own results include the HLA-A, B, and C types in 68 patients, the G1m and Km allotypes in 86 patients, and

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the frequencies of ABO blood groups in 126 patients with multiple myeloma. The allotype G1m(x) was significantly (p less than 0.05) more frequent in the patient group. Since the results in the literature on a possible HLA association have been inconsistent, all relevant available data were combined for an assessment of 379 patients vs 5,041 controls. In this comparatively large patient group, the previously reported increase of HLA-4c (HLA-B5 + B18 + Bw35) complex could be confirmed and identified as a weak (RR = 1.7) but significant (p less than 0.05) association of susceptibility to multiple myeloma with HLA-B5. Evaluation of G1m allotypes in the combined sample of 258 patients and 4,550 controls and Km in 179 and 2,457, respectively yielded no significant differences. (Author abstract) (40 Refs)

3. ANAEMIA IN PATIENTS WITH MYELOMATOSIS.

Ting WC, Cavill I, Jacobs A, Kaaba S, May A, Smith S, Whittaker JA

(c/o Jacobs) Dept. Haematology, Welsh Natl. Sch. Medicine, Heath Park, Cardiff CF4 4XN, Wales

Br J Cancer; 45(6):887-894 1982

Twenty-four untreated patients with myelomatosis were studied in order to characterize their anemia, using standard hematological and ferrokinetic techniques, together with measurements of circulating erythropoietin, erythropoietin sensitivity of marrow cultures and in vitro measurements of heme synthesis. There is a reduction in total erythroid output by the marrow, together with a minor degree of plasma expansion. In patients with normal renal function there is an appropriate increase in erythropoietin in response to anemia, but in a few cases there may be reduced response of CFU-E to the hormone in vitro. No abnormality of iron status or heme synthesis was found. One case of folate deficiency was discovered. (Author abstract) (30 Refs)

4. PROGNOSTIC FACTORS IN PLASMACYTOMA.

Meusers P, Konig E, Brittinger G

Hamatologische Abteilung der Medizinischen Klinik und Poliklinik, Universitat Essen (GHS), Hufelandstrasse 55, D-4300 Essen 1, W. Germany

Med Klin; 77(10):321-325 1982

Diagnosis of plasmacytoma requires that at least two of three criteria be met: greater than 20% atypical plasma cells in the bone marrow, evidence of monoclonal immunoglobulins in the blood and/or urine, and osteolysis. Prognosis depends on the type of immunoglobulin produced by the tumor. The types, in order of decreasing prognostic chances, include IgG, IgA, Bence-Jones kappa, Bence-Jones lambda, and IgD. The level of immunoglobulin and the presence or absence of anemia, renal failure, or osteolysis, when taken individually, are of little prognostic value. Prognosis becomes progressively unfavorable with increasing tumor size. One staging system correlates size with clinical factors and with evidence of renal failure. Among patients with tumors of the same size, prognosis depends on the [3H]thymidine labeling index (TLI). The av survival time for Group I (Stage I or II with a TLI less than 1%) is 68 mo; for Group II (Stage I or II with a TLI less than 1% or Stage III with a TLI less than 1%) 41 mo; fo Group III (Stage III with a TLI greater than 1%) 15 mo. Response to therapy cannot be predicted from prognostic factors, but requires in vitro or in vivo tests of the cytostatic agent. Prognosis in individual cases can be determined within 6 mo. (13 Refs) (In GER)

CLINICAL IMMUNOLOGY AND IMMUNOTHERAPY

5. FREE LIGHT CHAINS OF IMMUNOGLOBULINS IN SERUM FROM PATIENTS WITH LEUKAEMIAS AND MULTIPLE MYELOMA.

Solling K, Nielsen JL, Solling J, Ellegaard J

Dept. Medicine C, Aarhus Kommunehospital, DK-8000 Aarhus C, Denmark

Scand J Haematol; 28(4):309-318 1982

The serum concentration of free kappa and lambda light chains of immunoglobulins was measured in 114 patients with myelo- and lymphoproliferative disorders including multiple myeloma. Increased concentrations of a single light chain type, suggesting monoclonal origin, were found with high frequency in B-cell diseases only. Thus 6 out of 9 patients with chronic lymphatic leukemia and 24 of 28 patients with multiple myeloma had increased concentrations of a single chain type. The highest values reported in chronic lymphatic leukemia were approx 10 and in multiple myeloma 1,000x normal mean. Cytostatic treatment of chronic lymphatic leukemia was followed by a decrease in the light chain levels. The levels were, however, not correlated to the number of circulating lymphocytes, the lymphatic infiltration of tissue or clinical activity. Increased concentrations of both chain types, suggesting a polyclonal origin, were found in both of 2 patients with acute monocytic leukemia, 6 of 7 with acute myelomonocytic leukemia, 2 of 23 with acute myeloid leukemia and 1 of 7 with acute lymphoblastic leukemia. The highest levels of light chains in these groups were 5x normal mean. All patients with myeloproliferative disorders revealed normal values of both light chain types. (Author abstract) (24 Refs)

6. B-CELL NEOPLASMS WITH HOMOGENEOUS COLD-REACTING ANTIBODIES (COLD AGGLUTININS).

Crisp D, Pruzanski W

(c/o Pruzanski), Wellesley Hosp., 160 Wellesley St. East, Toronto, Ontario M4Y 1J3, Canada

Am J Med; 72(6):915-922 1982

Among 78 patients with persistent cold agglutinins, 31 had lymphoma, 13 had macroglobulinemia of Waldenstrom, six had chronic lymphocytic leukemia and 28 had chronic cold agglutinin disease. The average age was over 60 yr. Patients with chronic cold agglutinin disease had more hemolytic crises, bleeding and Raynaud's phenomena, and less frequently lymphadenopathy or hepatosplenomegaly. The frequency of anemia, positive Coombs test results, cryoglobulinemia and Bence Jones proteinuria was similar in the various groups. Survival time from diagnosis was on av 2 yr in lymphoma, 2.5 yr in Waldenstrom's macroglobulinemia, more than 6 yr in chronic lymphocytic leukemia and more than 5 yr in chronic cold agglutinin disease. Anti-I were common in chronic cold agglutinin disease and rare in other groups. Anti-I and other cold agglutinins were rare in chronic cold agglutinin disease and common in lymphoma and Waldenstrom's macroglobulinemia. In chronic cold agglutinin disease, and in Waldenstrom's macroglobulinemia, cold agglutinins usually had kappa light chains -92% and 71%, respectively - whereas in lymphoma, 71% of cold agglutinins had lambda light chains. The type of light chains related to the specificity of cold agglutinins. Cold agglutinins were cytotoxic to autologous and allogeneic lymphocytes. Occasionally, more autologous than allogeneic cells were killed implying that the former may be precoated in vivo with the antibodies. In conclusion, conditions with persistent

cold agglutinins are a spectrum that varies from 'benign' autoimmune-like chronic cold agglutinin disease to malignant lymphoma. Marked differences in the light chain type of cold agglutinins, specificity toward membranous antigens and severity of clinical manifestations were noted in benign and malignant varieties. (49 Refs)

7. A HUMAN MYELOMA CELL LINE THAT DOES NOT EXPRESS IMMUNOGLOBULIN BUT YIELDS A HIGH FREQUENCY OF ANTIBODY-SECRETING HYBRIDOMAS.

Pickering JW, Gelder FB
Dept. Microbiology and Immunology, Louisiana State Univ. Medical Center, P.O. Box 33932, Shreveport, LA, 71130
J Immunol; 129(1):406-412 1982

We selected an 8-azaguanine-resistant variant of a human myeloma cell line (RPMI 8226) by cloning the parental cells on a feeder layer of mouse spleen cells in the presence of increasing concentrations of 8-azaguanine. Culture media and cellfree extracts of both the parental and variant (8226 AR/NIP4-1) cell lines were assayed for production of immunoglobulin heavy and light chains by double immunodiffusion and for lambda-chain by radioimmunoassay. Secretion of free lambda-chain by the parental cell line was confirmed. In contrast, no immunoglobulin heavy or light chains were detected in culture medium of the variant cell line by either immunodiffusion or radioimmunoassay. No intracellular lambda-chain could be detected in the variant cells by radioimmunoassay of cellfree extracts or by immunofluorescence of fixed cells. Hybridomas were produced by fusion of 8226AR/NIP4-1 cells with lymphocytes from a mesenteric lymph node recovered at surgery from a hypertransfused renal transplant recipient. Twenty hybrid culture supernatants were assayed for immunoglobulin by double immunodiffusion, and 15 contained either IgG (lambda) or IgG (kappa). None produced IgM or IgA. An IgG (kappa)-producing hybridoma was shown by immunofluorescence not to express lambda-chain. A second fusion between the variant cell line and spleen cells from a renal transplant patient produced a stable hybridoma secreting IgM (lambda) antibody specific for the I antigen. (Author abstract) (30 Refs)

CHEMOTHERAPY

8. TREATMENT OF ADVANCED PLASMA CELL MYELOMA WITH WEEKLY CYCLOPHOSPHAMIDE AND ALTERNATE-DAY PREDNISONE.

Brandes LJ, Israels LG
Dept. Medicine, Univ. Manitoba, Manitoba Inst. Cell Biology, 100 Olivia St., Winnipeg, Manitoba, R3E 0V9, Canada
Cancer Treat Rep; 66(6):1413-1415 1982

Three of five patients with refractory myeloma were successfully palliated using a simple and relatively nontoxic regimen consisting of weekly cyclophosphamide in combination with alternate-day oral prednisone. Control of advanced disease in some patients may be associated with more frequent scheduling of known active drugs, even though these drugs, either alone or in combination, may not be effective when given at standard intervals of 4-6 wk. (Author abstract) (13 Refs)

9. PHASE III STUDY OF INTERMITTENT CARMUSTINE (BCNU) CYCLOPHOSPHAMIDE, AND PREDNISONE VERSUS INTERMITTENT MELPHALAN AND PREDNISONE IN MYELOMA.

Abramson N, Lurie P, Mietlowski WL, Schilling A, Bennett JM, Horton J
Suite 511, 820 Prudential Dr., Jacksonville, FL, 32207
Cancer Treat Rep; 66(6):1273-1277 1982

A prospective randomized trial in patients with previously untreated multiple myeloma was performed comparing carmustine (BCNU), cyclophosphamide, and prednisone (BCP) to melphalan (Alkeran) and prednisone (AP). Induction response rates, remission duration, and survival were similar with both regimens. Hematologic toxicity was greater with AP. Crossover studies in patients who relapsed did not illustrate any significant activity with either drug treatment program. Therefore, BCP can be utilized as initial therapy in myeloma because of comparable remission rates and less hematologic toxicity. (Author abstract) (14 Refs)

10. VINCRISTINE, BCNU, DOXORUBICIN, AND PREDNISONE (VBAP) COMBINATION IN THE TREATMENT OF RELAPSING OR RESISTANT MULTIPLE MYELOMA: A SOUTHWEST ONCOLOGY GROUP STUDY.

Bonnet J, Alexanian R, Salmon S, Bottomley R, Amare M, Haut A, Dixon D
Southwest Oncology Group, Operations Office, 4450 Medical Dr., San Antonio, TX, 78229
Cancer Treat Rep; 66(6):1267-1271 1982

A total of 151 patients with myeloma who had relapsed with or were resistant to melphalan and/or cyclophosphamide (Cytoxan) with prednisone received vincristine, carmustine (BCNU), doxorubicin (Adriamycin), and prednisone (VBAP) at 21-day intervals; 39 patients (25%) responded. Of the 123 patients with relapsing myeloma, 37 (30%) responded. Only two (7%) of the 28 patients with resistant myeloma responded. The regimen was well-tolerated in patients who had not had prior extensive irradiation. Thrombocytopenia was the most frequent form of toxicity. Survival was significantly longer in those patients responding to VBAP (median, 78 weeks) than in those not responding (median, 33 weeks) ($p = 0.002$). VBAP is a safe, effective regimen for patients with myeloma who relapse with alkylating agents. (Author abstract) (9 Refs)

11. PHARMACOKINETICS OF ORAL AND INTRAVENOUS MELPHALAN DURING ROUTINE TREATMENT OF MULTIPLE MYELOMA.

Bosanquet AG, Gilby ED
Dept. Clinical Investigation, Royal United Hosp., Combe Park, Bath, BA1 3NG, Avon, England
Eur J Cancer Clin Oncol; 18(4):355-362 1982

Plasma melphalan levels have been measured in nine (mostly Stage IIIA) multiple myeloma patients after therapeutic doses of drug had been given po and iv. A new isocratic high-pressure liquid chromatographic (HPLC) method with a sensitivity limit of 5 ng/ml was used to quantify the melphalan. Patients receiving 8-28.5 mg melphalan iv showed alpha and beta plasma decays with half-lives of 7.7 +-3.3 (mean +- SD) and 83 +-14 min respectively. The apparent volume of the central compartment was 12.8 +-4.3 l, and the total vol of distribution was 0.62 +-0.21 l/kg. Very variable absorption was seen in the same patients after receiving 5-12 mg melphalan po. The half-

life of the absorption phase varied from 2.1 to 62.1 min (22.8 +-18.1 min) with delays (before absorption started) of 0-113 min. The fraction of dose absorbed varied from 0.32 to 1.03 (0.72 +-0.23), and the half-life of the beta phase was 92 +-27 min. The type of breakfast eaten before po melphalan was found to correlate with the fraction of drug absorbed. (Author abstract) (27 Refs)

CASE REPORTS

12. A CASE OF IGE MYELOMA.

Kimura J, Suzuki N, Tomioka H, Takahashi H
Dept. Orthopedics, Sakura Natl. Hosp., Japan
Rinsho Ketsueki; 22(9):1469-1477 1981

IgE myeloma was diagnosed in a 71-yr-old woman who complained of right shoulder pain of 5-mo duration. Osteolytic and osteoporotic foci were observed with roentgenography in the skull, right scapula, and right ilium. Monoclonal protein was observed by means of cellulose-acetate electrophoresis in the fast gamma-region. The bone marrow was composed 53.6% of myeloma cells. The patient was treated with melphalan, cyclophosphamide, vincristine, nimustine hydrochloride, and prednisone. This is the sixth case of IgE myeloma reported in Japan and the fifteenth reported in the world. Characteristics of this case were compared to those in the other 14 cases. (21 Refs) (In JPN)

13. 'WALDENSTROM'S MACROGLOBULINEMIA' TERMINATING IN IMMUNOBLASTIC SARCOMA. A CASE REPORT.

Abe M, Takahashi K, Mori N, Kojima M
Dept. Pathology, Fukushima Medical Coll., 5-75 Sugitsuma-cho, Fukushima, 960, Japan
Cancer; 49(12):2580-2586 1982

An autopsy case of 69-yr-old man with Waldenstrom's macroglobulinemia terminating in immunoblastic sarcoma is reported. In the course of this case, the appearance of plasmocytoid lymphocytes was initially observed in peripheral blood smears and bone marrow punctures, but lymph node biopsy and bone marrow aspirations performed in the terminal stage, as well as autopsy, revealed a diffuse monotonous proliferation of immunoblasts in the lymphoreticular tissues. With the immunofluorescence method and PAP method Taylor, IgM kappa type of immunoglobulin was demonstrated in the cytoplasm of the proliferating cells, and the electron microscopic enzyme-labeled antibody technique identified localization of the immunoglobulin in the nuclear envelope and rough endoplasmic reticula of the immunoblasts. The results indicate that the initial appearance of plasmocytoid lymphocytes in this case and its terminal transformation into immunoblastic sarcoma are rare phenomena occurring in a single clone proliferation disorder of B-cell synthesizing IgM kappa immunoglobulins. (Author abstract) (21 Refs)

14. SOLITARY INTRACRANIAL PLASMACYTOMA: TWO PATIENTS WITH EXTENDED FOLLOW-UP.

Krumholz A, Weiss HD, Jiji VH, Bakal D, Kirsh MB
Div. Neurology, Sinai Hosp. Baltimore, Baltimore, MD, 21215
Ann Neurol; 11(5):529-532 1982

A 56-yr-old woman developed frontal headaches and blurred vision. At physical examination and laboratory tests signs of an avascular mass in the left temporal region were found. A 42-yr-old man showed clinical and laboratory evidence of an avascular mass in the right occipital lobe. Both patients had solitary intracranial plasmacytoma. The patients were followed for 13 and 8 yr, respectively, after biopsy and cranial irradiation. Neither of the patients developed recurrence or evidence of systemic myelomatosis. (14 Refs)

15. PLASMACYTOMA OF THE COLON. CASE REPORT WITH LAMBDA LIGHT CHAIN, DEMONSTRATED BY IMMUNOPEROXIDASE STUDIES.

Gleason TH, Hammar SP
Dept. Pathology, St. Frances Xavier Cabrini Hosp., Suite 505, 901 Boren Ave., Seattle, WA, 98104
Cancer; 50(1):130-133 1982

A case of solitary extramedullary plasmacytoma in the transverse colon of a 20-yr-old woman is reported. This case is unusual in that the plasmacytomas are only rarely observed in the gastrointestinal tract and are especially uncommon in the colon and in young women. The lesion was composed of pleomorphic plasma cells and contained areas of extracellular amyloid deposition. Its neoplastic nature was verified by the use of immunoperoxidase studies which were positive only for lambda light chain. The subject of gastrointestinal plasmacytomas and the use of immunoperoxidase studies on plasmacytic lesions are discussed. (Author abstract) (10 Refs)

16. EXTRAMEDULLARY PLASMACYTOMA OF THE BLADDER. A CASE REPORT AND REVIEW OF LITERATURE.

Yang C, Motteram R, Sandeman TF
Cancer Inst., 481 Little Lonsdale St., Melbourne, Victoria 3000, Australia
Cancer; 50(1):146-149 1982

A case report is presented of extramedullary plasmacytoma (EMP) of the bladder with pelvic and paraaortic nodal metastases. The patient was successfully treated with radiotherapy and cytotoxics. He survives 12 yr without evidence of disease. (Author abstract) (11 Refs)

17. ACUTE RENAL FAILURE FOLLOWING INTRAVENOUS PYELOGRAPHY (IVP) IN A PATIENT WITH DIFFUSE HYPERGAMMAGLOBULINEMIA: A CASE REPORT.

Antman KH, Parker LM, Goldstein JD, Skarin AT, D'Orsi CJ
(c/o Skarin), Sidney Farber Cancer Inst., 44 Binney St., Boston, MA, 02115
Med Pediatr Oncol; 10(3):289-294 1982

A 65-yr-old woman with polyclonal hypergammaglobulinemia developed acute renal failure requiring hemodialysis after an iv pyelogram (IVP). An increased risk of renal injury after IVP for patients with polyclonal hypergammaglobulinemia has not been previously recognized, although a parallel risk to patients with myeloma has been well established. At autopsy, immunoperoxidase staining of the bone marrow demonstrated plasma cell subpopulations with intracellular staining for IgG, IgA, and IgM and kappa and lambda light chains, proving that this patient did not have occult myeloma. Immunoperoxidase staining of casts in renal tubules also demonstrated polyclonal immunoglobulins. (Author abstract) (19 Refs)

18. MONOCLONAL GAMMOPATHY IN A 1-YR-OLD BOY WITH PROMYELOCYTIC LEUKEMIA (MEETING ABSTRACT).

Kreth HW, Gahr M
Institut fur Virologie und Immunobiologie, Universitat Wurzburg, Wurzburg, W. Germany
Onkologie; 4(5):280 1981

Monoclonal gammopathies have rarely been described in childhood up until now. We wish to report a case of a Turkish boy with recurrent infections who at the age of 1 yr was diagnosed as having promyelocytic leukemia. Serum immunoglobulin levels were above the normal range for his age before treatment was instituted. During the course of cytostatic therapy (combination of thioguanine, cytosine arabinoside, daunoblastine, vincristine sulfate and prednisone) a massive increase in the serum IgG fraction to a level greater than 5 g/deciliter was observed. Electrophoretic analysis revealed excessive amounts of a monoclonal, large basic protein of the IgG-lambda type. The monoclonal gammopathy described may be caused by 'derailment' and massive expansion of a B-cell clone as a result of suppression of immunologic control mechanisms during cytostatic therapy. On the other hand a common stem cell defect may be responsible for both disease manifestations (promyelocytic leukemia, monoclonal gammopathy). (no Refs) (In GER)

SELECTED PRE-CLINICAL STUDIES

19. CHANGES IN SUSCEPTIBILITY TO CYTOTOXIC ANTIBODY AMONG TUMOR CELLS SURVIVING EXPOSURE TO CHEMOTHERAPEUTIC AGENTS.

Shapiro SJ, Leibson PJ, Loken MR, Schreiber H
(c/o Schreiber), La Rabida-Univ. of Chicago Inst., East 65th St. at Lake Michigan, Chicago, IL, 60649
Cancer Res; 42(7):2622-2627 1982

We determined that myeloma cells which survived drug treatment had an altered sensitivity to cytotoxic antibody. The effects of several chemotherapeutic agents differing in drug action was compared. The antiserum was directed against viral determinants on the surface of S107 myeloma cells. This antiserum was then used to inhibit the colony formation of drug-treated myeloma cells. Tumor cells were treated with melphalan (200 ng/ml), methotrexate (40 ng/ml), actinomycin D (5 ng/ml), or 0.5 mM thymidine for 24 hr and then washed and resuspended in fresh medium. On various days after drug treatment, aliquots of these cells were exposed to complement and dilutions of antiserum and then cloned in soft agar in order to quantify the degree of antibody-mediated inhibition. Melphalan, methotrexate, and thymidine caused a severalfold increased resistance of the tumor cells to the antiserum during the first 1 or 2 days after drug treatment. During the following days, however, myeloma cells showed markedly increased susceptibility to the antiserum. The biphasic effects of methotrexate or thymidine treatment was similar to that previously observed after melphalan treatment and differed from the effect of actinomycin D. Actinomycin D caused only an increased susceptibility of the tumor cells to the antibody for a period of 4 to 5 days immediately following drug treatment. Our studies indicate that several chemotherapeutic drugs at concentrations comparable to those used in humans have long-lasting antagonistic as well as synergistic effects on the sensitivity of tumor cells to antibody and complement, depending on the particular drug used and on the time interval between drug exposure and subsequent treatment with antibody. These results suggest a model for evaluating the use of antibody in the elimination of malignant cells which, despite exposure to chemotherapy, remain clonogenic and proliferative. (Author abstract) (18 Refs)

20. PROLIFERATIVE STATE AND RADIOSENSITIVITY OF HUMAN MYELOMA STEM CELLS.

Shimizu T, Motoji T, Oshimi K, Mizoguchi H
(c/o Mizoguchi) Div. Hematology, Dept. Medicine, Tokyo Women's Medical Coll., 10 Kawada-cho, Shinjuku-ku, Tokyo 162, Japan
Br J Cancer; 45(5):679-683 1982

Human myeloma stem cells were detected by their capacity to form colonies in culture. Cells separated from aspirated marrow were cultured for 10 days in semi-solid methylcellulose with medium conditioned by T lymphocytes stimulated by phytohemagglutinin (PHA-TCM). The colonies formed consisted mostly of lymphoplasmacytoid cells or plasma cells, and the immunoglobulins in the patients' myeloma cells were demonstrated also in the cytoplasm of the colony cells. The number of colonies were proportional to the number of cells plated and to the concentration of PHA-TCM. When the proportion of proliferating colony-forming units of multiple myeloma (CFU-MM) was studied using the (3H)-dT-suicide technique, the high-specific-activity (3H)-dT killed 21-45% of the CFU-MM in 7 myeloma patients. According to a single dose of 60Co-gamma-irradiation, the mean doses for impairment of regeneration (Do) were 1.00 and 1.63 Gy in two cases, the extrapolation numbers being 1.6 and 2.0. (Author abstract) (6 Refs)

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SERIES CT13 No. 82/12

DECEMBER, 1982

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DIAGNOSIS

1. EXTRAMEDULLARY PLASMACYTOMA OF THE SMALL INTESTINE. A CASE REPORT STUDIED WITH ELECTRON MICROSCOPY AND IMMUNOPEROXIDASE TECHNIQUE.

Rygaard-Olsen C, Boedker A, Emus HC, Olsen HA
Inst. Pathological Anatomy, Frederiksborg County Central Hosp., DK-3400 Hillerod, Denmark
Cancer; 50(3):573-576 1982

A well-documented case of solitary extramedullary plasmacytoma located in the small intestine is presented. The patient underwent local resection of the tumor, and shows no signs of local recurrence or dissemination of the disease after a 5-yr follow-up. The pathologic nature of plasma cell tumors is discussed, and it is concluded that the demonstration of intracytoplasmatic immunoglobulin is essential for the exact classification of plasma cell neoplasms. (Author abstract) (13 Refs)

2. DIFFERENCES IN CLINICAL, MORPHOLOGIC AND CELL KINETIC PARAMETERS IN MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE (MGUS), SMOLDERING MULTIPLE MYELOMA (SMM) AND MULTIPLE MYELOMA (MM) (MEETING ABSTRACT).

Greipp PR, Kyle RA
Mayo Clinic and Foundation, Rochester, MN, 55901
Proc Am Soc Clin Oncol; 1:C-12 1982

Fifty-two patients with MGUS and SMM were compared with 23 patients with MM to see which parameters helped distinguish patients with overt MM. Plasma cell labeling indices (LI) were performed using high-speed scintillation auto-radiography. Morphologic studies were performed using Wright-stained direct marrow preparations and included assessment of

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plasma cell nucleolar size, grade and asynchrony. We found the LI to be the best diagnostic discriminant separating MGUS and SMM from MM. There was significant overlap between groups using other parameters. In three patients, initially classified as MGUS and SMM, MM developed within six months. Elevated LI alerted us to the diagnosis in all three. The LI is a reliable method which can be used in patients with MGUS and SMM who are difficult to differentiate from MM by standard clinical criteria. (1 Ref)

CLINICAL IMMUNOLOGY AND IMMUNOTHERAPY

3. TREATMENT OF LEUKEMIA AND LYMPHOMAS WITH INTERFERONS. I. TREATMENT OF MYELOMAS WITH HUMAN INTERFERON B.

Misset JL, Mathe G, Gastiaburu J, Goutner A, Dorval T, Gouveia J, Hayat M, Jasmin C, Schwarzenberg L, Machover D, Ribaud P, De-Vassal F, Horoszewicz JS
Service des Maladies Sanguines et Tumorales, Institut de Cancerologie et d'Immunogenetique, 12-16 avenue Paul-Vaillant-Couturier, 94800 Villejuif, France
Biomedicine; 36(1):55-59 1982

Eighteen patients with malignant gammopathies (16 with myeloma and 2 with Waldenstrom's disease) for a short time because in a Phase II-I trial were treated with human (IF beta) given iv 6 x 10(6) units weekly (7 patients) or 3 x 10(6) units twice weekly (11 patients) during at least 3 months if tolerated. Treatment was discontinued because of side-effects in three patients. Reduction of the M component of at least 25% from the initial value was obtained in three patients. In one case, was also observed the disappearance of a urinary Bence-Jones protein, in four cases a significant reduction of bone marrow infiltration by plasma cells and, in five cases, major alleviation or disappearance of bone pain. Length of treatment seems an important factor for activity. Immune monitoring with currently available tests, mainly NK cell activity, yielded no correlation with therapeutic effect in these patients. This very preliminary study demonstrates the effect of fibroblastic interferon in myeloma, but further studies are mandatory to determine the population of patients likely to benefit from treatment, the best modalities, possible special indication, dose schedule and duration of treatment. Interferon, however, already appears in this population of patients as giving results similar to those of single agent chemotherapy. As it is not myelosuppressive, it could be indicated in that frequent situation of advanced myeloma with bone marrow failure contraindicating combination chemotherapy. (Author abstract) (23 Refs) (In FRE)

4. USE OF IMMUNOGLOBULIN LIGHT CHAIN ANALYSIS TO DETECT BONE MARROW INVOLVEMENT IN B-CELL NEOPLASMS.

Sobol RE, Astarita RW, Chisari FV, Griffiths JC, Royston I
Dept. Medicine V-111E, Univ. California Sch. Medicine, La Jolla, CA, 92093
Clin Immunol Immunopathol; 24(1):139-144 1982

Double-blind analysis of bone marrow specimens from 15 patients with B-cell neoplasms and 10 controls was performed to determine whether immunoglobulin (Ig) light chain analysis (LCA) of bone marrow lymphoid cells is a more sensitive indicator of bone marrow involvement than light microscopic (LM) examination. Bone marrow aspirates were evaluated by a two-color immunofluorescence (IF) microscopic technique to determine the ratio of kappa-bearing lymphocytes to lambda-bearing lymphocytes (kappa/lambda ratio). Both bone marrow aspirate and biopsy specimens were reviewed by LM. Abnormal kappa/lambda ratios implied bone marrow involvement in 9/10 cases of non-Hodgkin's lymphoma (NHL), 4/4 cases of multiple myeloma (MM), and 1/1 case of Waldenstrom's macroglobulinemia (WM). All MM and WM cases had evidence for involvement by LM. Two NHL patients with abnormal kappa/lambda ratios had normal bone marrow morphology. LCA implied bone marrow involvement in 4/5 NHL patients with equivocal LM evaluations and in 3/3 cases with clear morphologic involvement. These data suggest that combined LCA and LM evaluation represent a more objective and inclusive method to detect bone marrow involvement in B-cell neoplasms than LM alone. (Author abstract) (14 Refs)

5. THE RATE OF IMMUNOGLOBULIN SUBCLASSES IN THE DIFFERENTIAL DIAGNOSIS OF MONOCLONAL GAMMOPATHIES.

Corrales A, San Miguel J, Lopez-Berges M, Hernandez F, Lopez Borrasca A
Servicio de Hematologia, Hosp. Clinico Universitario, Salamanca, Spain
Sangre (Barc); 27(2):165-171 1982

The rates of immunoglobulins and their subclasses were assessed in 45 multiple myeloma (MM) patients including 23 IgG-type paraproteins (17 IgG1, 2 IgG2 and 4 IgG3) and 22 IgA1-type paraproteins. Forty-seven patients with essential monoclonal gammopathies (EMG) were also studied, these begin comprised of 34 IgG paraproteins (26 IgG1, 5 IgG2, 2 IgG3 and 1 IgG4), 10 IgA1, and 3 IgM paraproteins, and a control group of people over 50 yr of age was also examined. A significant decrease of polyclonal immunoglobulin could be appreciated in the EMG group (p less than 0.001) which, as opposite to MM, was more important with respect to IgG and IgM. Hypogammaglobulinemia was most striking in the IgA EMG's, which could account for their worse prognosis. The levels of polyclonal immunoglobulins were significantly lower in the MM than in the EGM group (p less than 0.001). The rate of monoclonal IgG3 was low in both EMG and MM groups. Gamma 4 and gamma 2 were the most depressed polyclonal subclasses in EMG, whereas gamma 3 and gamma 1 were relatively preserved. The subclasses depression was more striking in the MM group, this being a factor which may help the differential diagnosis. (Author abstract) (22 Refs) (In SPA)

6. THE EFFECT OF ANTI-IA ANTIBODY ON IMMUNOGLOBULIN-SECRETING CELLS FROM HEALTHY INDIVIDUALS AND MYELOMA PATIENTS.

Nagai K, Nagai T, Takatsuki K, Uchino H
First Div., Dept. Internal Medicine, Faculty Medicine, Kyoto Univ., Kyoto, Japan
Scand J Immunol; 15(6):567-571 1982

Immunoglobulin-secreting cells (ISC) in the peripheral blood of healthy individuals and in the bone marrow, peripheral blood, or plasmacytomas of patients with multiple myeloma were enumerated by a protein-A plaque-forming cell assay after treatment with anti-Ia antibody and complement. Rabbit anti-human B-cell antisera and monoclonal anti-Ia antibody (OKIal) were used. By this treatment, the number of ISC in the peripheral blood of healthy individuals decreased to half, and that of M-protein-secreting cells from some patients with multiple myeloma also decreased markedly. In one patient, the number of M-protein-secreting cells in the bone marrow were

markedly reduced by this treatment, but this was not the case after 6 mo of chemotherapy, suggesting that the chemotherapy reduced chiefly the Ia-positive myeloma cells rather than Ia-negative myeloma cells. (Author abstract) (15 Refs)

CHEMOTHERAPY

7. TREATMENT OF ADVANCED PLASMA CELL MYELOMA WITH WEEKLY CYCLOPHOSPHAMIDE (C) AND ALTERNATE DAY PREDNISONE (P) (MEETING ABSTRACT).

Brandes LJ, Israels LG
Manitoba Cancer Treatment and Research Foundation, University of Manitoba, Winnipeg, Manitoba R3E 0V9, Canada
Proc Am Soc Clin Oncol; 1:C-739 1982

We report here on the successful palliation of 3 out of 5 patients with advanced myeloma, who either failed initially on melphalan and prednisone (MP), or who subsequently became refractory to MP and then to multiple drug regimens including vincristine (V), BCNU (carmustine) (B), and adriamycin (A) given at 3 to 4 week intervals. The present regimen consists of alternate day oral P (50-100 mg), and weekly low-dose intravenous C (150 mg-300 mg/M2; maximum weekly C 500 mg). All three responders experienced a decrease in M-protein of greater than 50%. One patient who was resistant to BAP and then developed a leukemic phase had a complete reversal on alternate day P weekly C, a second patient resistant to VBAP had reversal of hypercalcemia, and a third patient initially resistant to MP and then to VMCP had improvement in all parameters and stabilization of renal failure secondary to myeloma kidney. The subsequent survival of these three patients was 2 years, 14+ months, and 12+ months. (no Refs)

8. PROGNOSTIC FACTORS IN MULTIPLE MYELOMA TREATED WITH PREDNISOLONE AND SEQUENTIAL MELPHALAN AND IFOSFAMIDE: MIP COMBINATION CHEMOTHERAPY.

Adachi T, Asano K, Sezaki T, Takahashi I, Kimura I
Dept. Medicine, Okayama City Hosp., Okayama, Japan
Acta Med Okayama; 36(1):39-47 1982

Response rates and survival times were studied in 47 patients who had multiple myeloma and who were being treated with Prednisolone and sequential Melphalan and Ifosfamide (MIP therapy). The clinical response was determined by objective parameters such as the reduction of M-protein level, tumor vol and healing of bone destruction. Twenty-eight of the patients (59.6%) responded to the MIP therapy. The 50% survival time as followed from the initiation of treatment to death was 19 mo. Of the prognostic factors, the age (greater than or equal to 70 yr), clinical Stage III of Durie and Salmon, hypercalcemia, extensive bone lesions, and the patho-morphological Type IV of Brucher were associated with a decreased life-span. Therefore, MIP therapy was more effective in poor risk (high tumor mass group) than in good risk (low or intermediate tumor mass group) patients, but the survival of patients on MIP therapy was shorter in the poor risk group than in the good risk one. In addition, the group which responded rapidly (ie within 2-5 wk) had longer remission and longer survival than the group which improved slowly (ie after 6-16 wk). (Author abstract) (18 Refs)

CASE REPORTS

9. SOLITARY PLASMACYTOMA OF THE VERTEBRAL COLUMN. A REPORT OF 15 CASES.

Bacci G, Savini R, Calderoni P, Gnudi S, Minutillo A, Picci P
(c/o Picci) Istituto Ortopedico Rizzoli, Centro Tumori Ossei, Via Codivilla 9, 40136 Bologna, Italy
Tumori; 68(3):271-275 1982

The clinical features and the treatment results of 15 patients with solitary plasmacytoma of the spine observed in a 28-yr period (1950-1977) are reported. The signs at presentation were back pain in 4 cases and spinal cord compression in 11 cases. Three of these patients had paraplegia. Radiologically, the alteration encountered was an osteolytic lesion in all cases. The local treatment was radiotherapy in 11 cases and surgery plus radiotherapy in 4 cases. In three patients systemic chemotherapy was also employed. Seven patients are alive without signs of disease 3 to 9 yr (mean 6 yr) after diagnosis. Eight patients developed multiple myeloma in a period ranging from 1 to 8 yr (mean 3.5 yr). The relationship between multiple myeloma and solitary plasmacytoma of the spine, as well as the best treatment for the latter, are discussed. (Author abstract) (17 Refs)

10. PRIMARY GASTRIC PLASMACYTOMA WITH MASSIVE INTRACYTOPLASMIC CRYSTALLINE INCLUSIONS. A CASE REPORT.

Ferrer-Roca O
Departmento de Anatomia Patologica, Hospital Clinico Universitario Fuwltad de Medicina de la Laguna, Tenerife, Islas Canarias, Spain
Cancer; 50(4):755-759 1982

The case of a 75-year-old man with an extramedullary plasmacytoma of the stomach with peculiar histologic aspect is summarized. The cytoplasm of the proliferated cells was full of needle-shaped crystalline inclusions that made it difficult to recognize the plasma-cell nature. Under electron microscope, the crystalline inclusions were localized in the rough endoplasmic reticulum. They have a two internal line system of 75-85 A of period in a 45 degree angle with the main edge. The laser-ray analysis demonstrates that these two systems delineate hexagonal areas. (Author abstract) (28 Refs)

11. CHRONIC LYMPHATIC LEUKEMIA DEVELOPING IN A PATIENT WITH MULTIPLE MYELOMA. IMMUNOLOGIC DEMONSTRATION OF A CLONALLY DISTINCT SECOND MALIGNANCY.

Zalcberg JR, Cornell FN, Ireton HJ, McGrath KM, McLachlan R, Woodruff RK, Wiley JS
Dept. Hematology, Austin Hosp., Heidelberg 3084, Victoria, Australia
Cancer; 50(3):594-597 1982

A patient with multiple myeloma who subsequently developed chronic lymphocytic leukemia is reported. Initial studies demonstrated clinical and hematological features of multiple myeloma with an IgM lambda paraprotein. Skeletal disease was a significant presenting feature, although relapse occurred in extraosseous sites, particularly the pleura. He developed chronic lymphatic leukemia 31 mo later and immunological studies showed the malignant lymphocytes to have kappa light chain surface immunoglobulin, demonstrating separate clonal origin of this patient's two B-cell malignancies. (Author abstract) (23 Refs)

SELECTED PRE-CLINICAL STUDIES

12. IN VITRO PRODUCTION OF MONOCLONAL AND POLYCLONAL IMMUNOGLOBULINS BY PERIPHERAL BLOOD MONONUCLEAR CELLS IN HUMAN PLASMA CELL MYELOMA.

Peest D, Holm G, Mellstedt H, Pettersson D
Klinische Immunologie, Medizinische Hochschule Hannover, Postfach 610180, D 3000 Hannover 61, W. Germany
Scand J Immunol; 15(6):595-603 1982

The in vitro monoclonal and polyclonal immunoglobulin (Ig) production of peripheral blood mononuclear cells was studied in human multiple myeloma (4 IgG myelomas, 1 IgA myeloma) and in one patient with benign monoclonal gammopathy. Using an enzyme-linked immunosorbent assay with anti-class-specific antisera and antisera against idiotypic structures on the myeloma protein, it was possible to quantitate separately monoclonal and polyclonal Ig of the same class in cell culture supernatants. After stimulation with pokeweed mitogen (PWM) patients' cells produced lower amounts of polyclonal Ig than cells from healthy adults. In contrast, production of monoclonal Ig could not be enhanced by PWM. Moreover, the kinetics of monoclonal Ig production was different from that of polyclonal Ig. Myeloma cells contained large amounts of monoclonal Ig while their content of polyclonal Ig was low. A rapid release of preformed monoclonal Ig during the 1st day of culture was not inhibited by puromycin. A later phase of release was partly suppressed by puromycin and was probably caused by active protein synthesis. (Author abstract) (27 Refs)

13. DEVELOPMENT OF RESISTANCE TO MOPC-315 PLASMACYTOMA AFTER INTRALESIONAL AND INTRAPERITONEAL MELPHALAN THERAPY OF TUMOR-BEARING BALB/C MICE. I. ENHANCEMENT OF IN VIVO REJECTION RESPONSES BY COMBINED CHEMOTHERAPY-IMMUNOTHERAPY.

Adler A, Altbaum I
Tumor Immunology Unit, Inst. Oncology, Beilinson Medical Center, Petah Tiqva, Israel
JNCI; 68(6):963-969 1982

Experimental and clinical evidence indicates that some chemotherapeutic agents may enhance tumor cell immunogenicity. This study was undertaken to test the possibility that melphalan [L-phenylalanine mustard (L-PAM)], a clinically useful drug, can modulate tumor cells in vivo and in vitro in a syngeneic experimental system of MOPC-315 plasmacytoma in BALB/c mice and that this modulation can be expressed in vivo by enhanced tumor resistance. Tumor-bearing mice were treated with L-PAM intralesionally and ip by a split-course chemotherapy to avoid excessive toxicity of the drug. As a result of this treatment, about 60% of the mice had complete tumor regression; of these, 40-60% were resistant to viable tumor cell challenge and were designated as cured-immune.' Immunogenicity of irradiated MOPC-315 was tested in BALB/c mice; significant protection against tumor cell challenge was not achieved. In vitro L-PAM-treated MOPC-315 cells induced a measurable but weak antitumor response. Combination of both therapeutic approaches, ie, chemotherapy and active immunization by L-PAM-treated tumor cells, was attempted with the use of various schedules. Immunotherapy given after L-PAM-induced tumor regression significantly enhanced in vivo antitumor response to challenge by 10(4) and 10(5) viable MOPC-315 tumor cells. When immunotherapy was attempted before chemotherapy in the presence of actively growing though still occult tumor, it reduced the chemotherapy cure rate and resulted in a low rate of tumor resistance. Addition of BCG did not remarkably affect the results. The findings point to the importance of timing of active immunization relative to tumor load and chemotherapy. The implication is that chemotherapy-induced regression is mediated by host immune mechanisms in this experimental model. (Author abstract) (19 Refs)

14. HYBRIDOMAS THAT SECRETE MONOCLONAL ANTIBODIES AGAINST HUMAN NORMAL AND CANCER CELLS (MEETING ABSTRACT).

Lee LS
General Electric Research and Development Center, Schenectady, NY, 12301
Hybridoma; 1(2):225 1982

A human lung-carcinoma-derived cell line was used to produce antibodies against tumor-associated antigens. About 10(7) cells which were frozen and thawed once, were injected ip into a female Balb/C mouse once per week for 4 weeks. The spleen of the mouse was removed and the lymphocytes were purified and fused with the mouse myeloma cell line SP2/0. Optimal hybridization was obtained when the hybridization cultures were exposed to Carbowax 3350 for a total of 10 min. A solid phase enzyme-linked immunoassay was employed to screen 67 hybridoma supernatants for reactivity with normal and tumor cells grown in monolayers. The results suggest that normal membrane antigens may become nondetectable on cancer cells because they are misplaced inside the cells. Similarly, tumor antigens may arise from the dislocation of normal intracellular antigens onto the cell surface. Cell surface antigen loss, as well as neoantigen appearance, both detectable by monoclonal antibodies, may both be useful in the immunodiagnosis of cancer. (no Refs)

15. MONOCLONAL ANTIBODIES TO A HUMAN PROSTATE ANTIGEN.

Frankel AE, Rouse RV, Wang MC, Chu TM, Herzenberg LA
Cetus Immune Corporation, 3400 West Bayshore Drive, Palo Alto, CA, 94305
Cancer Res; 42(9):3714-3718 1982

Three monoclonal antibodies reactive with a purified extractable Mr 34,000 prostate antigen (PA) have been prepared by fusing splenocytes of BALB/c mice preimmunized with purified PA with the NS1 mouse myeloma cell line. The three antibodies were all of the IgG-1 subclass. The antibodies defined two noncross-blocking unique determinants on PA; each present as one site per molecule. IF3 defined on antigenic site and 2G7 and 1C5 defined another antigenic determinant. All of the antibodies reacted with PA in a solid-phase radioimmunoassay and immunoprecipitated 125I-labeled PA. Absorption and sandwich radioimmunoassays showed PA in prostate tissues but not in tonsil, liver, or kidney. Immunoperoxidase staining of formalin-fixed paraffin-embedded sections of benign prostatic hyperplasia and prostatic carcinoma revealed strong prostate epithelial reactivity. None of the antibodies showed reactivity with prostate membrane preparations. A sandwich radioimmunoassay used 2G7 as a plate coat. 125I-labeled 1F3 was used to detect 5 ng PA per ml in sera of patients with prostate cancer. These results confirm previous observations regarding the specificity of PA and shed new evidence for its intracellular localization. (Author abstract) (17 Refs)

16. IDENTIFICATION OF AN ONCOFETAL ANTIGEN (GP90) ON MURINE B16 MELANOMA CELLS.

Nishio C, Ishii Y, Ishii K, Kikuchi K
(c/o Ishii) Dept. Pathology, Sapporo Medical Coll., S1 W17, Sapporo 060, Japan
Eur J Cancer Clin Oncol; 18(6):579-588 1982

A xenoantiserum to murine B16 melanoma cells was developed by immunizing rabbits with cultured B16 melanoma cells. This antiserum could, after extensive absorption with normal C57BL/6 mouse tissues, react with syngeneic (B16) and allogeneic (HP) melanomas as well as with other murine neoplasms, including syngeneic 75S adenocarcinoma, allogeneic myeloma and leukemic T cell lines. The antiserum also cross-reacted with syngeneic fetal fibroblasts and with an allogeneic fetal fibroblast cell line (SC-1) either uninfected or infected with murine leukemia virus (MuLV). Immunoprecipitated material from B16 melanoma cell-surface glycoproteins that had been labeled with [125I] by lactoperoxidase and purified by a Lentil lectin column was analyzed by one-dimensional SDS- and two-dimensional polyacrylamide gel electrophoresis, which disclosed an acidic glycoprotein with a molecular weight (mol wt) of 90 K daltons. Absorption studies suggested that the 90 K mol wt glycoprotein represented the oncofetal moiety expressed in murine melanoma, carcinoma and fetal tissues. When the amount of this antigen in developing C57BL/6 mouse fetuses was measured by absorption assays, we found that it was expressed strongly in those fetuses just before birth. Binding and absorption studies demonstrated that the 90 K mol wt glycoprotein, while being expressed on a variety of fetal and neoplastic cells in mice, did not exist at detectable levels in normal tissues of adult C57BL/6 mice, including tissues of the thymus, lymph node, spleen, liver, brain, lung and kidney. (Author abstract) (26 Refs)

17. SOMATIC VARIANTS OF MURINE IMMUNOGLOBULIN LAMBDA LIGHT CHAINS.

Bothwell AL, Paskind M, Reth M, Imanishi-Kari T, Rajewsky K, Baltimore D
Center for Cancer Res., Massachusetts Inst. Technology, Cambridge, MA, 02139
Nature; 298(5872):380-382 1982

The nucleotide sequences of lambda complementary DNA clones, two lambda 1 genes from hybridomas and a lambda 2 gene from a myeloma, were determined. It was demonstrated that somatic mutations in lambda chains do not have to be localized in the complementarity-determining regions (CDR), as they can occur in both the framework and the CDR residues. (25 Refs)

18. EFFECTS OF IMMUNOGLOBULIN STRUCTURE ON FC RECEPTOR BINDING: A MOUSE MYELOMA VARIANT IMMUNOGLOBULIN WITH A GAMMA2B-GAMMA2A HYBRID HEAVY CHAIN HAVING A COMPLETE GAMMA2A FC REGION FAILS TO BIND TO GAMMA2A FC RECEPTORS ON MOUSE MACROPHAGES.

Birshtein BK, Campbell R, Diamond B
Dept. Cell Biology, Albert Einstein Coll. Medicine, Bronx, NY, 10461
J Immunol; 129(2):610-614 1982

We report here the primary structure of an immunoglobulin heavy chain synthesized by ICR 16, a variant of the MPC 11 mouse myeloma cell line. The ICR 16 heavy chain is a gamma2b-gamma2a hybrid, consisting of the CH1 domain of gamma2b and the hinge, CH2, and CH3 domains of gamma2a subclasses. The genetic mechanism by which ICR 16 occurred may be recombination, based on homologies in both coding and intervening sequences in gamma2b and gamma2a constant region genes. Although the Fc fragment of ICR 16 is completely gamma2a-like and has been shown to bind to gamma2a Fc receptors on mouse macrophages, the intact H2L2 molecule is unable to do so. Such an observation underscores the crucial role that conformation may play in the ability of immunoglobulins to carry out biologic functions. (Author abstract) (41 Refs)

19. NON-IMMUNOGLOBULIN-ASSOCIATED DNA REARRANGEMENTS IN MOUSE PLASMACYTOMAS.

Harris LJ, Lang RB, Marcu KB
(c/o Marcu) Biochemistry Dept., State Univ. New York at Stony Brook, Stony Brook, NY, 11794
Proc Natl Acad Sci USA; 79(13):4175-4179 1982

We have characterized a class of DNA rearrangements in plasmacytomas. These recombination events involve a DNA sequence whose origin is outside of the locus of the heavy chain constant region genes, CH. Therefore, we choose to refer to this sequence as non-immunoglobulin-associated rearranging DNA (NIARD). We have isolated two abortively rearranged C alpha genes, generated by NIARD events from the alpha-producing J558 myeloma. Restriction endonuclease maps of these sequences reveal two possible recombination sites in NIARD that are separated by approx 6.5 kilobase pairs of DNA (defined at 5' and 3' sites). A NIARD rearrangement occurs in 15 out of 20 plasmacytomas tested, including gamma3-, gamma1, gamma2b-, gamma2a-, and alpha-producers, but this event usually does not involve a CH switch (S) region. In fact, only S alpha appears to accept NIARD. However, NIARD did not undergo a rearrangement in eight IgA-producing hybridomas tested. One germ-line copy of NIARD (a 22-kilobase pair EcoRI fragment) is retained in all plasmacytomas. NIARD does not appear to possess repetitive DNA sequences homologous to S mu or S alpha. We discuss the possible role and implications of NIARD-like sequence rearrangements in allelic exclusion and chromosomal translocation events in plasmacytomas. (Author abstract) (30 Refs)

20. INTERACTION OF EPSTEIN-BARR VIRUS WITH LEUKAEMIC B CELLS IN VITRO. II. CELL LINE ESTABLISHMENT FROM PROLYMPHOCYTIC LEUKAEMIA AND FROM WALDENSTROM'S MACROGLOBULINAEMIA.

Finerty S, Rickinson AB, Epstein MA, Platts-Mills TA
Dept. Pathology, Medical Sch., Univ. Bristol, Bristol, England
Int J Cancer; 30(1):1-7 1982

Leukemic B-cell populations were prepared from six patients with high-count prolymphocytic leukemia (PLL) as well as from one patient with Waldenstrom's macroglobulinemia (WM) in frankly leukemic phase, and their response to in vitro Epstein-Barr (EB) virus infection was monitored in terms of expression of the virus-associated nuclear antigen EBNA and of virus-induced transformation to continuous cell lines. The individual leukemic populations, tested on several occasions, gave reproducibly different responses one from another which were not obviously related to differences either of surface immunoglobulin phenotype or of immunoglobulin secretor status in vivo. After infection, four out of six PLL populations showed either transient or a more persistent expression of EBNA, always involving a minority of the cells, with no evidence of any virus-induced transformation up to 6 wk. In con-

trast, two out of six PLL samples as well as the WM sample rapidly gave rise to EBNA-positive cell lines which, on the evidence both of restricted immunoglobulin class expression and of abnormal marker chromosomes, were clearly derived from the leukemic cells. Further comparative studies of such leukemic B-cell populations may help to define host cell components necessary for the triggering of EB-virus-induced cellular transformation. (Author abstract) (32 Refs)

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